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AMERICAN MEDICAL ASSOCIATION

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A.M.A. ARCHIVES OF
PATHOLOGY

Geriatric Pathology

Autopsy Findings in Three Hundred Fifty-Six Persons Eighty Years of Age and Older

R. M. MULLIGAN, M.D., Denver

"The sum of our years is seventy, and if we are strong, eighty."—Psalm 90, Verse 10.

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Submitted for publication April 22, 1959.

Department of Pathology, University of Colorado School of Medicine.

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Introduction

In view of the increased life span of both sexes with each passing year, an evaluation

of the fatal diseases of old age should be available to the practicing physician. By learning the frequency and characteristics of diseases observed in geriatric patients, he could anticipate their treatment at an earlier and more amenable stage. Useful longevity would then be promoted within the limits of the desires and resources of the individual and of the community. Once the appraisal of such diseases is made by review, a more thorough approach to them could be made by preview by means of the subsidized autopsy, as suggested recently (Angrist, 1957 [2]). Combined data from many medical centers in this and other countries would then become available to form the basis for the attack on the problems of aging, which become progressively more important to the physician and his patient as each lives through successive decades. The paucity in the literature of pathologic-anatomic data, the basis for the appreciation of any disease, on the causes of death in geriatric patients has prompted a study of the autopsies made on persons 80 years of age and older and representing deaths from all causes at the Colorado General Hospital in the 15-year period between 1940 and 1955.

Materials and Methods

In the study of each case in this series, the clinical features, the gross description, and the microscopic sections were reviewed. Clinicopathologic correlation was stressed. Frequently, the anatomic diagnoses were completely rearranged in the order of importance most logical in relation to the available facts and to the categories of disease surveyed. Tissues were nearly always fixed in Zenker's fluid and stained with hematoxylin and eosin or other dyes, as indicated by the nature of the pathologic lesions. The usual tissues examined were thyroid, thymus, heart, coronary arteries, aorta, lungs, spleen, esophagus, stomach, intestine, appendix, liver, gallbladder, pancreas, adrenals, kidneys, bladder, prostate, testes (or uterus, tubes, ovaries, vagina), lymph nodes, and vertebral marrow. Brain, pituitary, and spinal cord were usually examined when it was clinically indicated. Parathyroid glands were not included unless confirmed microscopically. Structures such as other arteries and veins, bile ducts, ureters, seminal vesicles, epididymides, pleura, pericardium, peritoneum, nerves, skeletal muscle, and soft tissue were studied microscopically as indicated. Lesions not producing complications or insignificant by themselves were not counted. These included inconsequential rheumatic scarring of endocardium of myocardium, nonocclusive arteriosclerosis of arteries, mild pulmonary edema or bronchopneumonia, healed tubercles of lungs or bronchial lymph nodes, partial adhesions of pleura, pericardium, or peritoneum, obliterative fibrosis of the appendix, small hernias or hydroceles, accessory spleens, and minimal nodular changes in the prostate.

Observations

A survey made at Colorado General Hospital between July 1, 1940, and July 1, 1955, revealed 4,483 deaths, 2,758 of males and 1,725 of females, exclusive of the newborn and stillborn. Of the 3,396 autopsies, 2,119 were on males, or a rate of 76.8%, and 1,277 were on females, or a rate of 74.0%. During this period 356 persons, 253 men and 103 women 80 years of age and older were autopsied; 325 were 80 to 89 years of age, and 31 were 90 and older. These 356 persons accounted for 10.5% of the 3,396 autopsies.

In Table 1, these autopsies are arranged according to semidecades for patients under 70, 70-79, and 80+ years of age. Persons under 70 showed a progressive percentage decline; those 70-79 years of age, a moderate increase, and those 80+ years of age, a steady and striking increase, indicating a trend toward more autopsies on patients in the last age group in this hospital, a trend probably related to the increase in

TABLE 1.—*Autopsies by Semidecades at Colorado General Hospital, 1940-1955 Exclusive of Newborn and Stillborn*

Years	1940-1955	1940-1945	1945-1950	1950-1955
Number	3,396	1,058	1,131	1,207
Age, yr.	Under 70	759 71.7%	757 66.9%	742 61.5%
	70-79	220 20.8%	267 23.6%	295 24.4%
	80+	79 7.5%	107 9.5%	170 14.1%

TABLE 2.—*Principal Causes of Death in 356 Persons 80 Years of Age and Older Autopsied at Colorado General Hospital, 1940-1955*

Cause of Death	Total	Per Cent	Male	Female
Cardiovascular disease	132	37.0	92	40
Essential hypertension	66	18.5	48	18
Arteriosclerosis	43	12.1	29	14
Other cardiovascular disease	23	6.4	15	8
Amyloidosis of heart	7	2.0	7	0
Embolism of lungs	6	1.7	5	1
Calcification of heart valves	3	0.8	1	2
Congenital aneurysm of cerebral arteries	2	0.6	0	2
Miscellaneous	5	1.4	2	3
Cancer	58	16.3	44	14
Infection	44	12.4	35	9
Accident	43	12.1	19	24
Nodular hyperplasia of prostate	29	8.1	29	--
Alimentary tract diseases	20	5.6	14	6
Diabetes mellitus	6	1.7	3	3
Nervous system diseases	2	0.6	2	0
Respiratory tract diseases	2	0.6	1	1
Unsatisfactory cases	20	5.6	14	6
	356	100.0	253	103

the life span now evident in the United States.

The 356 autopsies in this series are outlined in Table 2 according to the principal cause of death and the sex. The relative frequency of cardiovascular disease, cancer, infection, accident, nodular hyperplasia of the prostate, alimentary tract diseases, diabetes mellitus, nervous system diseases, and respiratory tract diseases in the 336 satisfactory cases of this series was as follows: 64, 29, 22, 21.5, 14.5, 10, 3, 1, 1.

The 20 unsatisfactory cases were excluded for the following reasons: inadequate protocols, 7; protocols missing, 6; protocols and slides adequate without a definite cause of death being established, 5, and partial autopsy, 2.

The ratio between men and women in the 336 satisfactory cases was 2.45. A detailed analysis of these cases will be given in the order indicated in Table 2. Following this, associated diseases and lesions contributing to death or of correlative importance will be summarized.

A. Cardiovascular Diseases

Essential Hypertension.—Sex and Age: Of 66 persons dying of essential hypertension (Bell and Clawson, 1928 [7]), 48 were men and 18 were women, or a ratio of 3.67; 63 were 80 to 89 years of age, and 3 were 90 years of age and older.

Cardiac Hypertrophy: The weights, in grams, of the hearts of these 66 persons were as follows: 351 to 400 gm., 8; 401 to 450 gm., 18; 451 to 500 gm., 15; 501 to 550 gm., 9; 551 to 600 gm., 12; 601 to 650 gm., 3, and 651 to 700 gm., 1. Of the eight with hearts weighing 351 to 400 gm., the body

TABLE 3.—*Percentage Figures in Column 5 Represent the Chances of a Person with a Given Disease Listed in Column 1 of Dying of This Disease in 304 of the 336 Satisfactory Cases*

Disease	Principal Cause of Death	Contributory or Incidental	Total	Percentage of Lethality
Essential hypertension	66	14	80	82.5
Arteriosclerosis				
Coronary arteries	25	22	47	53.2
Cerebral arteries	9	15	24	37.5
Arteries, lower extremities	4	10	14	28.6
Pulmonary arteries	3	0	3	100.0
Superior mesenteric artery	1	1	2	50.0
Arteriosclerotic aneurysm, aorta	1	5	6	16.7
Amyloidosis, heart	7	11	18	38.8
Embolism, lungs	6	64	70	8.6
Cancer	58 *	30	88	65.9
Bronchopneumonia	31	60	91	34.1
Accident	43	24	67	64.2
Nodular hyperplasia, prostate	29	54	83	34.9
Cholecystitis	4	34	38	10.5
Peptic ulcer	9	11	20	45.0
Appendicitis	2	0	2	100.0
Diabetes mellitus	6	2	8	75.0

* Six of these patients also had one incidental cancer not included in the 30 listed in Column 3.

weight was 37.6 to 68.4 kg. and the height was 143 to 171 cm. in seven; in one the weight and height were not recorded. Body weight was correlated in these and in the remaining patients whose heart weighed 401 to 700 gm. in such a manner that significant cardiac hypertrophy was present in each (Rosahn, 1941 [27]). Dilatation of the heart, determined by valve measurements, was observed in 41 cases, or 62%. Miscellaneous features of these 66 hearts included fibrosis of the myocardium of the left ventricle, 8; mural thrombosis of the right atrium, 6; focal necrosis of the myocardium of the ventricles, 2; an old infarct of the left ventricle, 1; old and recent infarcts of the left ventricle, 1, and mural thrombosis of both atria, 1. Significant coronary arteriosclerosis and embolism of pulmonary or systemic arteries were not observed in association with any of these miscellaneous features.

Arteriosclerosis of Coronary Arteries: This lesion (Schlesinger and Zoll, 1941 [28]) was observed in 22 patients, 16 men and 6 women. In 18 patients these arteries showed significant stenosis by atheroma, which involved both coronary arteries in 6, the anterior descending branch of the left coronary artery in 4, the posterior descending branch of the right coronary artery in 4, the left coronary artery in 2, and the right coronary artery in 2. Of the remaining four cases, thrombosis was observed in three (in two with occlusion of the anterior descending branch of the left coronary artery and in one with occlusion of the left coronary artery) and hemorrhage in an atheroma of the left coronary artery in one.

Of these 22 cases, infarcts of the left ventricle were seen in 17, in 13 of which they were old, in 3 old and recent, and in 1 recent, perforated, and accompanied by hemopericardium (250 cc.). Of the remaining five cases, fibrosis of the myocardium of the left ventricle was observed in four and a recent infarct of the right ventricle in one.

Of these 22 cases, mural thrombosis of the left ventricle was found in 5, acute fibrinous pericarditis in 2, and mural thrombosis of both ventricles in 1. Pulmonary or systemic dissemination of emboli was absent in these cases.

Edema of the Lungs: This lesion was moderate to severe in 33 patients, 27 men and 6 women. Minor pulmonary edema in several other cases was not included.

Hydrothorax: Of 27 patients, 24 men and 3 women, hydrothorax was bilateral in 22, left-sided in 4, and right-sided in 1. Of the 22 bilateral cases, the average amount of serous fluid, in cubic centimeters, in either pleural cavity was as follows: less than 500 in 2 cases; 501 to 1,000 in 14; 1,001 to 1,500 in 5; and 1,501 to 2,000 in 1. Ascites, with 200 to 1,200 cc. of fluid, was seen in 7 of the 22 bilateral cases.

Passive Hyperemia of the Liver: This lesion, in 21 patients, 17 men and 4 women, was acute in 12 and chronic in 9.

Recent Hemorrhage: Of five patients, three men and two women, significant bleeding involved the lungs in three, the intestine and uterus in one, and the stomach in one.

Embolism of Lungs: This lesion (Hunter et al., 1941 [14]; Towbin, 1954 [33]) contributed to death in all 12 patients affected, 7 men and 5 women. The embolus was small in three, medium in six, and large in three. Recent pulmonary infarcts were associated in three cases: mural thrombosis of the right atrium, in two, and massive collapse of a lung, in one.

In all sections in which embolism of the lungs has been analyzed, a small embolus indicates plugging of small pulmonary artery branches of one or two lobes of the lungs; a medium embolus, plugging of the pulmonary artery branch to one or two lobes, and a large embolus, plugging of one or both major arteries to the lungs.

Other Embolism: In three cases embolism was associated with mural thrombosis of the left atrium of the heart, as follows:

CASE 1.—Man, 82. Embolism of superior mesenteric arteries; early gangrene of intestine.

CASE 2.—Woman, 86. Embolism of splenic artery; recent infarcts of spleen.

CASE 3.—Woman, 83. Embolism of right subclavian artery; gangrene of right upper extremity.

Brain Lesions: Of the 66 cases, the brain was not examined in 29, was examined and found not remarkable in 21, and was examined and showed lesions in 16. Of these 16 patients, 12 men and 4 women, 9 showed significant arteriosclerosis of cerebral arteries with stenosis in 5, thrombosis in 3, and perforation in 1. The associated eight infarcts and one hemorrhage were recent in seven and old in two patients, and were medium in seven, small in one, and large in one. The distribution of these associated lesions was as follows: a parietal lobe, three; a temporoparietal area, one; a temporal lobe, one; an occipital lobe, one; basal ganglia, one; pons, one, and a cerebral hemisphere, one. The remaining 7 of these 16 patients did not show significant cerebral arteriosclerosis, but displayed the following lesions: infarcts of the brain, 4; subdural hematoma, 2, and a large hemorrhage, 1. The four infarcts were as follows: recent large infarct of a cerebral hemisphere; recent medium infarct of the basal ganglia; old medium infarct of the basal ganglia, and recent medium infarct of a temporoparietal area.

Arteriolosclerosis of Kidneys: Of the 66 cases, 53, or 80.3%, 40 men and 13 women, showed this lesion (Moritz and Oldt, 1937 [20]), which consisted of moderate to severe hypertrophy of the media of the arterioles of the kidneys, notably the afferent arterioles of the glomeruli; of variable hyalinization of the altered media, and of stenosis of the lumen. No case of slight involvement of the renal arterioles was included. In no instance was necrotizing arteriolitis observed. In practically all kidneys of the 66 cases, the small, medium, and large arteries showed variable fibroelastic thickening of the intima.

Other Cardiovascular Lesions: In 24 patients, 19 men and 5 women, 26 assorted cardiovascular lesions included the following: arteriosclerotic mural thrombosis of the aorta, 6; infarct of the spleen, 5 (recent, 4; old, 1); gangrene of a lower extremity three hours to six years following midthigh amputation and related to arteriosclerotic thrombosis of a popliteal artery, 4; recent infarct of a kidney, 3; patent foramen ovale, 2, and arteriosclerotic aneurysms of aorta and hypogastric arteries, early gangrene of the large intestine not due to obvious arterial thrombosis, early gangrene of the small intestine due to thrombosis of the superior mesenteric artery, recent infarct of a lung not due to obvious arterial thrombosis, thrombosis of an esophageal vein, and organized thrombosis of the pulmonic artery, 1 each.

Infection: Among 28 patients, 24 men and 4 women, 34 inflammatory lesions included cystitis, 9 (chronic, 7; acute 1; subacute, 1); early bronchopneumonia, 8; moderate to severe bronchopneumonia, 6; acute ulcerative esophagitis, 4; lipid pneumonia, 3, and acute bronchitis, acute enteritis, acute ulcerative gastritis, and active tuberculosis of the adrenals and epididymis, 1 each.

Alimentary Tract Lesions: Among 39 patients, 26 men and 13 women, 53 lesions were observed, as follows: calculi of the gallbladder, 11; atrophy of the liver, weight 780 to 980 gm., 10; chronic cholecystitis, 7; diverticula of the intestine, 6; acute central necrosis of the liver, 4; hernia, 3; chronic ulcer of the duodenum, 2; cirrhosis of the liver, 2; fat necrosis of the pancreas, 2; fatty metamorphosis of the liver, 2; melanosis coli, 2; calculi of the common bile duct, 1, and hypoplasia of the gallbladder, 1.

Of the 11 patients with calculi of the gallbladder, 9 were men and 2 were women. The calculi were multiple in 10 (pigment type in 3) and solitary in 1.

Of the seven patients with chronic cholecystitis, four were men and three were women. Calculi were multiple in six and absent in one.

Of the six cases of intestinal diverticula, the lesions were observed in the large intestine in three, in the small intestine in two, and in the jejunum (Meckel's) in one; they were multiple in four cases and solitary in two.

Two hernias were inguinal, and one was diaphragmatic. One chronic ulcer of the duodenum was perforated and associated with peritonitis. In one case liver cirrhosis was cardiac; in the other, portal.

Benign Tumors: Among 7 women and 5 men, the 16 benign tumors included 7 polyps (3 of the large intestine, 2 of the cervix, and 2 of the endometrium), 4 leiomyomas (2 of the stomach, 1 of the hypodermis, and 1 of the uterus), 2 adenomas (1 of the adrenal cortex and 1 of a parathyroid gland), 2 cysts (1 of a kidney and 1 of the peritoneum), and 1 duct papilloma of the breast.

Nonlethal Cancers: Among 13 men, 8 showed carcinoma of the prostate, and, of these and 1 woman, carcinoma of the duodenum (peripapillary), esophagus, kidney, large intestine, liver, and stomach were represented by 1 case each.

Nodular Hyperplasia of Prostate: This lesion was significant in 17 patients, 10 of whom showed hypertrophy of the urinary bladder and 1 a diverticulum. Seven had undergone operation seven months to four years previously—suprapubic resection, four; transurethral resection, two, and cystostomy, one.

Miscellaneous Lesions: Fifty-two miscellaneous lesions, present in 33 patients, 23 men and 10 women, included the following: operative absence of organs, 12; atrophy of the testes, 4; hospital accidents, 4; calculus of the urinary bladder, 3; decubital ulcers, 3; obliterative fibrous pleuritis, 3, and hydronephrosis, hypoplasia of a kidney, obesity, and minimal silicosis of the lungs, 2 each. One example of each of the following was observed: atrophy (weight 1 gm.) of an adrenal gland; atrophy (weight 980 gm.) of the brain; calculus of the bronchus of the middle lobe of the right lung; congenital dislocation of the right hip; diabetes mellitus with atrophy and hyalinization of pancreatic islets; an intertrochanteric fracture of the femur sustained at home; bilateral hydrocele (150 cc. of fluid each); hydropericardium (100 cc. of fluid); hydrosalpinx; hypoplasia of bone marrow; old infarct of right cerebral hemisphere, clinical; myeloid hyperplasia of bone marrow; nodular goiter, weight 110 gm.; ossification of right epididymis, and chronic granulomatous salpingitis.

The surgically removed organs (12 cases) included the gallbladder, 5 cases; the appendix, 3 cases, and the stomach, uterus, tubes, and ovaries, 1 case each. One patient who had cholecystectomy also showed two medium abscesses of the liver along the gallbladder bed. One patient had partial gastrectomy and gastroenterostomy. All operations were performed years before death. Atrophy of the scrotal testis was bilateral in two cases and right-sided in one; atrophy affected the inguinal testes of one patient. The four hospital accidents were as follows: fracture of left ribs; fracture of the neck of the left femur; aspiration of gastric content into the lungs, and hemorrhage into the right psoas muscle, related to misdirection of a spinal needle.

Summary of Sixty-Six Cases of Essential Hypertension: In this series of 66 cases of essential hypertension in persons 80 years of age and older, about 3 of 4 were men. With respect to hypertrophy of the heart, 58 patients had hearts weighing 401 to 700 gm.; in these 58 patients and in the remaining 8 with hearts weighing 351 to 400 gm., adjustment with body weight indicated that the cardiac hypertrophy was significant. Dilatation of the heart occurred in 41 of these 66 cases, or 62%. Of the 22 cases with arteriosclerotic stenosis or thrombosis of coronary arteries, old infarcts or fibrosis of the myocardium of the left ventricle of the heart was found in 21. Evidences of cardiac failure included edema of the lungs, in 33 cases; bilateral hydrothorax, in 22 cases, usually with 500 to 1,500 cc. of fluid

on a side; acute or chronic passive hyperemia of the liver, in 21 cases, and recent hemorrhage of viscera, in 5 cases. Embolism of the lungs contributed to death in 12 cases. Embolism of systemic arteries was associated with mural thrombosis of the left atrium of the heart in three cases. Of the 16 cases in which the brain was examined and found to contain lesions, 9 showed arteriosclerotic stenosis, thrombosis, or perforation of cerebral arteries associated with recent infarction or hemorrhage of the brain. The brains of seven other patients did not show significant arteriosclerosis, but did display infarction, subdural hematoma, or hemorrhage. Of the 66 cases, 53 showed moderate to severe arteriolosclerosis of the kidneys. A cardiovascular lesion variably contributing to death was infarction of the spleen, lower extremities, kidneys, or intestine, the infarction being related to obvious arteriosclerotic stenosis or thrombosis in some instances. Moderate to severe bronchopneumonia contributed to death in six cases. Other lesions, such as esophagitis, acute central necrosis of the liver, and accidental injuries, were less common features contributing to death.

Arteriosclerosis.—Sex and Age: Of the 43 persons dying of arteriosclerosis and its sequelae, 29 were men and 14 were women, or a ratio of 2.07; 39 were 80 to 89 years of age, and 4 were 90 years of age and older.

Principal Site of Arteriosclerosis: Among these 43 cases, the most important site of arteriosclerosis was in the coronary arteries, in 25; the cerebral arteries, in 9; the arteries of the lower extremities, in 4; the pulmonary arteries, in 3; the superior mesenteric artery, in 1, and the aorta, in 1.

Arteriosclerosis of Coronary Arteries: This lesion (Schlesinger and Zoll, 1941 [28]) was observed in 25 patients, 17 men and 8 women. In 19 patients these arteries showed significant stenosis by atheroma; in 6 cases they exhibited thrombosis, organized in 4. Among these 25 cases, both coronary arteries were involved in 11, the anterior descending branch of the left coronary artery in 6, the left coronary artery in 3, the circumflex branch of the left coronary artery in 2, the right coronary artery in 2, and the posterior descending branch of the right coronary artery in 1.

Of these 25 cases, 21 showed myocardial lesions as follows: old infarct of the left ventricle, in 8; recent infarct of the left ventricle, in 4; recent perforated infarct of the left ventricle, in 3; recent infarct of the right ventricle, in 1; old infarct of the interventricular septum, in 1, and fibrosis of the myocardium of the left ventricle, in 4. Of the seven cases of recent infarct of the left ventricle, two also had old infarcts of the left ventricle.

Among these 25 cases, dilatation of the heart was found in 12, hypertrophy of the heart (weight at 420 to 570 gm.) in 4, and hemopericardium (100 to 435 cc.) in 3. Mural thrombosis of the right atrium occurred in three; of the left atrium, in two; of the right atrium and the ventricles, in one; of the right atrium and left ventricle, in one, and of the left atrium, in one. One patient with mural thrombosis of the left ventricle had clinical embolism of the right popliteal artery and gangrene of the right leg and foot. Two patients also had significant amyloidosis of the heart.

Arteriosclerosis of Cerebral Arteries: This lesion (Dublin, 1954 [12]) was observed in nine patients, five men and four women. In seven patients these arteries showed significant stenosis; in one, thrombosis, and in one, perforation. One or more cerebral arteries were affected in four cases, the left middle cerebral in two, the right middle cerebral in one, the left internal carotid and left middle cerebral in one, and the internal carotid and basilar in one. In eight patients, recent cerebral infarcts were distributed as follows: right cerebral hemisphere, in two, and left cerebral hemisphere, right frontoparietal area, left parietal lobe, one occipital lobe, one occipital lobe and the pons, and right parietal lobe and occipital lobe, in one each. The infarcts were

large in three cases and were medium in five. One patient with an infarct of the left cerebral hemisphere also had small recent right frontal and right cerebellar infarcts. The ninth patient had a large recent hemorrhage of the left cerebral hemisphere.

Arteriosclerosis of Other Arteries: Of these nine cases, the arteries of the lower extremities were affected in four, the pulmonary arteries in three, the superior mesenteric artery in one, and the aorta in one.

Cases 1-4.—The four men with arteriosclerosis of arteries of the lower extremities (Bell, 1950[8]) showed thrombosis in two and occlusion by atheroma in two. The right popliteal artery was affected in two; the right femoral, in one, and the right posterior tibial, in one. Three showed gangrene of a leg and foot, and one, gangrene of the foot only. Two had had a midthigh amputation several days before; one, a right middle toe amputation two months before, and one had had no surgical procedure.

Cases 5-7.—The three men with arteriosclerosis of the pulmonary arteries (Brenner, 1935[9]) had thrombosis involving the pulmonic artery in the first, the right pulmonary artery in the second, and both pulmonary arteries in the third. Their hearts showed hypertrophy of the right chambers, with weight at 360 to 400 gm. and the thickness of the right ventricle at 10 to 14 mm. Two had dilated hearts.

Case 8.—Woman, 83. Arteriosclerotic stenosis, superior mesenteric artery; gangrene and hemorrhage, small intestine.

Case 9.—Man, 80. Arteriosclerotic aneurysm, 10 cm., fusiform, thrombosed, perforated, abdominal segment of aorta; hemoperitoneum (800 cc.); hemorrhage, retroperitoneum; recent 1 cm. infarct, left kidney.

Edema of Lungs: This lesion was moderate to severe in 16 patients, 13 men and 3 women.

Hydrothorax: In 15 patients, 10 men and 5 women, hydrothorax was bilateral in 13, left-sided in 1, and right-sided in 1. Of the 13 bilateral cases, the average amount of serous fluid, in cubic centimeters, in either pleural cavity was as follows: less than 500 in 7 cases, 501 to 1,000 in 4 cases, 1,001 to 1,500 in 1 case, and 1,501 to 2,000 in 1 case. Ascites (200 to 500 cc. of fluid) was seen in two cases.

Passive Hyperemia of Liver: This lesion in 10 patients, 7 men and 3 women, was acute in 6 and chronic in 4.

Embolism of Lungs: This lesion contributed to death in all nine patients affected, seven men and two women. The embolus was small in five patients, medium in two, and large in two. Recent pulmonary infarcts were associated in six cases; mural thrombosis of the right atrium, in two; thrombosis of the right femoral vein, in one, and mural thrombosis of right atrium and ventricle, in one.

Brain Examination: Of the 43 cases, the brain was not examined in 17, was examined and found negative in 12, and showed lesions in 14. (See section above: Arteriosclerosis of Cerebral Arteries; see sections below: Other Cardiovascular Lesions and Miscellaneous Lesions.)

Other Cardiovascular Lesions: In 20 patients, 13 men and 7 women, 26 assorted cardiovascular lesions included the following: recent infarct of kidney, in 4; infarct of the spleen, in 4 (recent in 3 and old in 1); arteriosclerotic stenosis or occlusion of a coronary artery, in 3, with old infarct of the left ventricle of the heart in 2 and dilatation of the heart in 1; arteriosclerotic mural thrombosis of the aorta, in 3; arteriolosclerosis of the kidneys, in 2, and hemorrhage of the lungs, in 2. The following lesions occurred in one case each: arteriosclerotic aneurysm of the ascending thoracic segment of the aorta; arteriosclerotic stenosis of cerebral arteries with old small infarcts of the left occipital lobe, right basal ganglia, and cerebellum; arteriosclerotic stenosis of superior mesenteric artery with gangrene of the ileum; arteriosclerotic thrombosis of femoral and popliteal arteries with gangrene of the feet 36 days following bilateral midthigh amputation of the lower extremities; fibrosis of the endocardium of the right atrium; old small infarcts of the cerebral hemispheres; thrombosis of the right middle cerebral artery, and partly organized thrombosis of the left common iliac vein.

Infection: Among 23 patients, 15 men and 8 women, 34 inflammatory lesions included moderate to severe bronchopneumonia, in 11 (bilateral in 8, right-sided in 2, and left-sided in 1); cystitis, in 8 (chronic in 7 and acute in 1); early bronchopneumonia, in 5; abscess, in 2 (left perinephric in 1 and of the left ureter in 1); acute ulcerative esophagitis, in 2, and aspirative bronchopneumonia, acute ulcerative colitis, chronic myocarditis, acute prostatitis, acute left-sided pyelonephritis, and acute ulcerative urethritis, in 1 each.

Alimentary Tract Lesions: Among 25 patients, 13 men and 12 women, 29 lesions included the following: atrophy of the liver, weight 850 to 1,000 gm., 7; diverticula of the intestine, 7; calculi of the gallbladder, 6; chronic cholecystitis, 2; uncomplicated hernia, 2, and cardiac cirrhosis of the liver, chronic ulcers (2) of the duodenum, fatty metamorphosis of the liver, left inguinal hernia with incarceration and early gangrene of the large intestine, and hyalinization of the pancreatic islets, in 1 each.

The seven cases of diverticulum of the intestine were observed as follows: large intestine, five, duodenum, one, and the ileum (Meckel's) one; they were multiple in five cases and solitary in two.

Of the six patients with calculi of the gallbladder, four were men and two were women. The calculi were multiple in all six cases and of pigment type in four.

The two cases of chronic cholecystitis occurred in women. Calculi were multiple in both cases. In one case the calculi were of pigment type and were also found in the common bile duct.

The two uncomplicated hernias were inguinal and umbilical, respectively.

Benign Tumors: Among six patients, 2 men and 4 women, the eight benign tumors included four polyps—two of the stomach, one of the endometrium, and one of the large intestine—two leiomyomas—one of the stomach and one of the jejunum—one cystadenoma of the pancreas, and one hemangioma of the liver.

Nonlethal Cancers: Two men had carcinoma of the prostate; in one the tumor extended to the urinary bladder and seminal vesicles. One woman showed a carcinoma of the endometrium.

Nodular Hyperplasia of the Prostate: This lesion was significant in eight patients, five of whom showed hypertrophy of the urinary bladder, two, diverticula of the urinary bladder, and two, recent infarcts of the prostate. No patient had had a previous operation.

Miscellaneous Lesions: These lesions numbered 33 in 19 patients, 12 men and 7 women, and included decubital ulcers, 5; accidental injuries, 4; calculi of the male genitourinary tract, 3; operative absence of the appendix, 2; atrophy of the brain, weight at 980 and 1,060 gm., 2; atrophy of the testes, 2; collapse of the lungs, 2, and minimal silicosis of the lungs and bronchial lymph nodes, 2. Single examples of the following were recorded: cyst of the right kidney; edema of the larynx; emphysema of the lungs; nodular goiter, weight 160 gm.; hydrosalpinx; right hydrocele, 220 cc. of fluid; static hyperplasia of the endometrium; left-sided obliterative fibrous pleuritis; ptosis of the right kidney; scoliosis of the thoracic spine, and stricture of the right ureter with hydronephrosis.

Two accidents sustained at home resulted in intertrochanteric fracture of the right femur 34 days and 2 years, respectively, following open reduction. Two hospital accidents resulted in hemorrhage of the right frontoparietal region of the scalp and in abrasions of the skin of the face and trunk. The genitourinary calculi affected the urinary bladder of one man and the urinary bladder and prostate of another. The lower lobes of the lungs and the left lung were collapsed in one case each.

Summary of Forty-Three Cases of Arteriosclerosis: Of 43 persons dying of arteriosclerosis and complications, about 1 out of 2 were men. The most important site of arteriosclerosis was in the coronary arteries, in 25; the cerebral arteries, in 9;

the arteries of the lower extremities, in 4; the pulmonary arteries, in 3; the superior mesenteric artery, in 1, and the aorta, in 1. The coronary arteries showed significant arteriosclerotic stenosis or thrombosis in 25 cases, of which 19 showed old or recent infarction or fibrosis of the myocardium of the left ventricle, 12 showed dilatation of the heart, and several others showed hemopericardium, mural thrombosis of one or more chambers of the heart, or amyloidosis of the heart. The nine patients with arteriosclerotic stenosis, thrombosis, or perforation of cerebral arteries revealed recent medium or large infarction or hemorrhage of the brain. The four patients with arteriosclerotic thrombosis or occlusion of arteries of the lower extremities showed gangrene of the leg and foot on the affected side. The three patients with arteriosclerotic thrombosis of pulmonary arteries showed hypertrophy of the right cardiac chambers. The one patient with a stenosed arteriosclerotic superior mesenteric artery had gangrene and hemorrhage of the small intestine. The one patient with a large arteriosclerotic aneurysm of the aorta showed perforation of the aneurysm and severe peritoneal hemorrhage. Evidences of cardiac failure were moderate to severe edema of the lungs, in 16 cases; bilateral hydrothorax, in 13 cases, the fluid usually averaging 500 to 1,000 cc. on a side, and acute or chronic passive hyperemia of the liver, in 10 cases. Embolism of the lungs contributed to death in nine cases. Of the 26 cases in which the brain was examined, 14 showed lesions, including the 9 summarized above and 5 others exhibiting atrophy of the brain, old infarcts of the cerebral hemispheres, or cerebral arterial thrombosis without infarction. A cardiovascular lesion variably contributing to death was infarction of the kidneys, myocardium of the left ventricle of the heart, spleen, intestine, or lower extremities, related to obvious arteriosclerotic stenosis or thrombosis in some instances. Moderate to severe bronchopneumonia contributed to death in 11 cases. Other lesions, such as abscesses, acute ulcerative lesions of alimentary or urinary tract, and cardiac cirrhosis of the liver, were less common contributing factors in causing death.

Other Cardiovascular Diseases.—Amyloidosis of Heart: Of seven men, 80 to 89 years of age, in whom this disease (Mulligan, 1958[21]) was the cause of death, the following lesions were found: dilatation of the heart, in 7; edema of the lungs, in five; hypertrophy of the heart, weight 485 to 680 gm., in four; hydrothorax, 500 to 1,000 cc. of fluid, in 3 (bilateral in 2 and left-sided in 1); passive hyperemia of the liver, in 3 (chronic in 2 and acute in 1); pericarditis, in 3 (obliterative fibrous in 2 and acute fibrinous in 1); chronic cholecystitis, in 2, with multiple calculi in 1; fibrosis of the myocardium of the left ventricle of the heart, in 2, and nodular hyperplasia of the prostate, in 2, with hypertrophy of the urinary bladder in 1. The brain was not examined in six cases and was examined and found to be negative in one. One patient who had right inguinal herniorrhaphy with release of two fibrous strictures of the ileum shortly before death also had a left inguinal hernia incarcerating the sigmoid segment of the large intestine. Single examples of the following were observed: abscess of the upper lobe of the left lung; absence of the right testis; ascites, with 1,000 cc. of fluid; aspiration of gastric contents into the lungs; atrophy of the liver, weight 945 gm.; atrophy of the left testis; bronchopneumonia; portal cirrhosis of the liver; a 9 cm. cyst of the left kidney; acute ulcerative gastritis; nodular goiter, weight 75 gm.; myeloid hyperplasia of the bone marrow; patent foramen ovale; minimal silicosis of lungs and bronchial lymph nodes; mural thrombosis of the atria of the heart, and perforated chronic ulcer of the duodenum.

Embolism of Lungs: This lesion was the only discerned principal cause of death (Hunter et al., 1941[14]; Towbin, 1954[33]) in six patients, five men and one woman; five were 80 to 89 years of age, and one

was 98. The emboli were large in three, medium in two, and small in one. No source for the pulmonary emboli was determined in these six cases. Recent pulmonary infarcts were found in five, bronchopneumonia in two, dilatation of the heart in two, cystitis in two (acute in one, chronic in one), and leiomyoma in two (uterus in one, stomach in one). The brain was not examined in three cases and was examined and found to be negative in three cases. Single instances of the following were noted: abscess of the right lung, calculus of the gallbladder, carcinoid tumor of the ileum metastatic to the liver, an 11 cm. cyst of the right kidney, edema of the lungs, acute passive hyperemia of the liver, nodular hyperplasia of the prostate with hypertrophy of the bladder six years following transurethral resection, patent foramen ovale, polyp of the stomach, and quadricuspid pulmonic valve.

Calcification of Heart Valves: Three cases, two with involvement of the aortic valves (Karsner and Koletsky, 1947 [16]) and one with involvement of the mitral valve are summarized.

Case 1.—Man, 84. Calcification, aortic valve, heart; dilatation, aortic valve; hypertrophy, heart, weight 750 gm.; fibrosis, myocardium, left ventricle; dilatation, heart; mural thrombosis, right atrium, heart; embolism, pulmonary artery, left lung; infarct, small, recent, left lung; hemorrhage, lungs and intestine; hydropericardium, 220 cc. fluid; hydrothorax (right, 900 cc. fluid; left, 500 cc.); chronic passive hyperemia of the liver; cardiac cirrhosis, liver; ascites, 500 cc. of fluid; brain examined and found negative.

Case 2.—Woman, 80. Calcification, aortic valve, heart; stenosis, aortic valve; hypertrophy, heart, weight 550 gm.; dilatation, heart; mural thrombosis, right atrium, heart; hydrothorax, right, 700 cc. fluid; collapse, lower lobe, right lung; embolism, pulmonary arteries; infarcts, multiple, recent, lungs; bronchopneumonia, early; serous cyst, 5 cm., left ovary; brain examined and found negative.

Case 3.—Woman, 89. Calcification, mitral valve, heart; stenosis, mitral valve; mural thrombosis, left atrium, heart; bronchopneumonia, early; hydrothorax (right, 1,000 cc. fluid; left, 300 cc.); acute passive hyperemia, liver; atrophy, liver, weight 840 gm.; chronic cystitis; brain not examined.

Congenital Aneurysm of Cerebral Arteries: Two cases (McDonald and Korb, 1939 [18]) were as follows:

Case 1.—Woman, 81. Aneurysm, congenital, ruptured, right internal carotid and posterior communicating arteries; hemorrhage, 10 cm., right cerebral hemisphere and left lateral ventricle; edema, lungs; hemorrhage, urinary bladder; calculus, 18 mm., gallbladder; polyp, 7 mm., sigmoid segment, large intestine; leiomyomas, 25 mm., uterus.

Case 2.—Woman, 88. Aneurysm, congenital, ruptured, basilar, left posterior cerebral, and left superior cerebellar arteries; hemorrhage, subarachnoid, ventricles, midbrain, and pons; edema, lungs; atrophy, liver, weight 950 gm.; fatty metamorphosis, moderate, liver.

Miscellaneous: The following five cases, not categorized readily with any of the preceding groups, are summarized.

Case 1.—Woman, 82. Embolism, superior mesenteric artery; atrial fibrillation, clinical; gangrene, small intestine; gangrene, cecal and ascending segments, large intestine; acute fibrinopurulent peritonitis; hemorrhage, lungs and urinary bladder; nodular hyperplasia, cortex, adrenal glands (right, weight 12.5 gm.; left, weight 23 gm.); adenoma, 8 mm., islet-cell, tail, pancreas; laparotomy scars (2); absence of gallbladder, appendix, uterus (supracervical), tubes, and ovaries; brain removed and not sectioned; left hemiparesis, clinical.

Case 2.—Woman, 87. Chronic rheumatic endocarditis; stenosis, mitral valve, heart; mural thrombosis, atria, heart; embolism, right pulmonary artery; infarcts, recent, right kidney and left adrenal; embolism, right popliteal artery, clinical; gangrene, right foot; bronchopneumonia; hydrothorax, left, 300 cc.; hospital accident, fracture, intertrochanteric, right femur, 17 days following open reduction; wound, recent, skin, left hip; acute ulcerative duodenitis; atrophy, liver, weight 870 gm.; leiomyomas (4), 7 to 35 mm., uterus; obliterative fibrous pleuritis, right; brain not examined.

Case 3.—Man, 81. Cavernous hemangioma, 4 cm., right side, midbrain and pons; hemorrhage, right side, pons; cavernous hemangiomas (2), 1 cm., left frontal lobe and right side, midbrain; bronchopneumonia, aspirative; dilatation, heart; decubital ulcers (3), 4 cm., skin, sacrum and buttocks; cystostomy, four months previously; cavernous hemangioma, left adrenal; amyloidosis, left adrenal; nodular hyperplasia, prostate; arteriosclerotic mural thrombosis, aorta; fatty metamorphosis, moderate, liver.

Case 4.—Man, 86. Hemorrhage, recent, right temporoparietal, brain; bronchopneumonia; embolism, pulmonary artery, upper lobe, right lung;

nodular hyperplasia, prostate; hypertrophy, urinary bladder; diverticula, urinary bladder; chronic suppurative cystitis; cyst, 8 cm., left kidney; chronic cholecystitis; hydrops, 100 cc.; gallbladder; adenoma, 1 cm., chromophobic, pituitary gland; diverticula, descending segment, large intestine.

CASE 5.—Woman, 91. Infarcts (2), recent, right parietal lobe, 7 cm., and right occipital lobe, 2 cm., brain; bronchopneumonia, partly organized; amyloidosis, heart; atrophy, liver, 1,000 gm.; chronic cystitis; polyp, 1 cm., endometrium.

B. Cancer

Sex and Age.—Of 58 persons dying of cancer, 44 were men and 14 were women, a ratio of 3.14; 53 were 80 to 89 years of age, and 5 were 90 to 99 years of age. One man had two primary cancers contributing to death.

Primary Site of Cancer.—The primary sites of 59 cancers in these 58 patients were as follows: prostate, 16; stomach, 7; large intestine, 6; skin, 5; hematopoietic system, 4; lungs, 4; pancreas, 4; breast, 3; pharynx, 3, and cystic duct, urinary bladder, jejunum, larynx, liver, palate, and thyroid gland, 1 each. The gastric cancers were in the antrum in five cases and in the cardia in one case, and the site was not stated in one case. The cancers of the large intestine were in the rectum in five cases and in the transverse segment in one case. The skin cancers were on the face in three cases, on a hand in one case, and on the abdomen in one case. The four lung cancers involved the main bronchi, the right lower lobe, the left upper lobe, and the left lower lobe. The cancers of the pancreas were in the body and tail in two cases, in the body in one case, and in the tail in one case. All three mammary cancers involved the left breast. The cancer of the larynx was beneath the right vocal cord of the patient with thyroid cancer who had had x-radiation to the primary tumor of the thyroid gland one year before death.

Type of Cancer.—Of the 59 cancers, 55 were carcinomas, 2 were lymphocytic lymphosarcomas, 1 was a plasma-cell myeloma, and 1 was myelogenous leukemia.

The 55 carcinomas were as follows: 28 adenocarcinomas of the cystic duct, large intestine, lungs, prostate, and stomach; 9 squamous-cell carcinomas of the larynx, palate, pharynx, and skin; 6 duct carcinomas of the breast and pancreas; 3 undifferentiated carcinomas of the jejunum and lungs; 2 mucous-cell carcinomas of the stomach; 2 papillary carcinomas of the urinary bladder and thyroid gland; 2 unclassified carcinomas of the stomach; 1 acinar carcinoma of the pancreas; 1 case of Bowen's disease of the skin, and 1 liver-cell carcinoma.

Infection.—Among 31 patients, 26 men and 5 women, 48 inflammatory lesions included moderate to severe bronchopneumonia, in 14 cases; cystitis, in 14 (chronic, in 10; chronic suppurative, in 2, and subacute, in 2); pyelonephritis, in 8 (chronic, in 3; chronic suppurative, in 3, and acute, in 2); abscess, in 2 (lower lobe of right lung and pelvis); acute ulcerative esophagitis, in 2, and syphilitic aortitis, acute cholangitis, acute ulcerative colitis, acute ulcerative enteritis, acute fibrinous pericarditis, lobar pneumonia, acute left pyelitis, and miliary tuberculosis of mediastinal and cervical lymph nodes, in 1 case each. Bronchopneumonia was bilateral in 11 cases and right-sided in 3. Pyelonephritis was bilateral in four cases, right-sided in three cases, and left-sided in one case.

Cardiovascular Lesions.—Among 29 patients, 24 men and 5 women, 41 lesions included embolism of the lungs, 11 cases; hypertrophy of the heart (weight 400 to 540 gm.), 8; arteriosclerosis of the coronary arteries, 6; arteriosclerotic mural thrombosis of the aorta, 3; essential hypertension, 3; amyloidosis of the heart, 2; arteriosclerosis of cerebral arteries, 2; thrombosis of iliac veins, 2, and, in 1 case each, arteriosclerotic stenosis of right popliteal artery with gangrene of right leg and foot two weeks following midthigh amputation, calcific stenosis of the aortic valve with hypertrophy of the heart (weight 400 gm.) and edema of the lungs, mural throm-

bosis of the right atrium of the heart, and thrombosis of the splenic artery.

Embolus of the lungs was large in five cases, medium in four cases, and small in two cases; this lesion contributed to death in these 11 cases, in none of which was a source for the emboli demonstrated.

Of the six cases of arteriosclerosis of the left coronary artery or of the anterior descending branch of this artery, stenosis, in four, and thrombosis, in two, were associated with old infarct of the left ventricle of the heart, in four, and fibrosis of the myocardium of the left ventricle, in two. Other lesions were dilatation of the heart, in two, mural thrombosis of the left ventricle of the heart, in two; edema of the lungs, in one, and bilateral hydrothorax (right, 800 cc., and left, 1,500 cc.), in one.

In all three cases of essential hypertension, hypertrophy of the heart to weights of 350, (body weight, 36.3 kg.; height, 149 cm.), 450, and 580 gm.; edema of the lungs, and arteriolosclerosis of the kidneys were observed. Dilatation of the heart and bilateral hydrothorax (right, 300 to 1,500 cc.; left, 300 to 700 cc.) were found in two cases. Arteriosclerotic thrombosis of the right coronary artery was accompanied by an old infarct of the left ventricle of the heart and a recent infarct of the right ventricle in one case. Hemorrhage into atheromas of the arteriosclerotic right coronary artery and the anterior descending branch of the left coronary artery was accompanied by an old infarct of the left ventricle of the heart and chronic passive hyperemia of the liver in one case.

One patient with amyloidosis of the heart also showed small amyloid deposits in pancreatic, adrenal, and seminal vesical blood vessels.

Of the two cases of cerebral arteriosclerosis, one showed arterial stenosis, with a recent left occipitoparietal infarct of the brain, and one showed thrombosis of the right middle and posterior cerebral arteries, with a recent right frontoparietal infarct of the brain.

Thrombosis of the iliac veins was bilateral in one case and right-sided in one.

Alimentary Tract Lesions.—Among 27 patients, 15 men and 12 women, 39 lesions of the alimentary tract were found as follows: calculi of the gallbladder, 10; diverticula of the intestine, 8; chronic cholecystitis, 6; atrophy of the liver (weight 750 to 1,000 gm.), 5; acute central necrosis of the liver, 2; fat necrosis of the pancreas, 2; chronic ulcer of the stomach, 2, and calculus of the common bile duct, calculus of the pancreatic duct, left inguinal hernia with gangrene of the incarcerated descending and sigmoid segments of the large intestine, and chronic ulcer of the duodenum, 1 each.

The calculi of the gallbladder were multiple in eight cases and solitary in two.

The diverticula of the intestine, multiple in six cases and solitary in two, involved the large intestine in four, the duodenum in two, and the small intestine in two.

Of the six cases of chronic cholecystitis, three showed multiple calculi; one, a solitary calculus, and two, no calculi; one case also had empyema of the gallbladder.

Benign Tumors.—Among 17 patients, 13 men and 4 women, the 19 benign tumors included 5 cysts, 2 of the kidneys and 1 each of the thymus (ectopic in right cervical region), pituitary, and arachnoid of the cerebrum; 5 polyps, 2 of the large intestine and 1 each of the cervix, endometrium, and stomach; 4 leiomyomas, 2 of the stomach, 1 of the ileum, and 1 of the uterus; 2 carcinoid tumors of the small intestine, and cystadenoma of a kidney, hemangioma of the liver, and pancreatic heterotopia of the jejunum, 1 each.

Nonlethal Cancers.—Six patients, five men and one woman, had nonlethal cancers. Two had squamous-cell carcinoma of the skin; one had an infiltrating duct carcinoma of the breast, successfully excised by radical mastectomy 43 years before; one had an acinar carcinoma of the tail of the pancreas; 1 had an adenocarcinoma of the rectum, and 1 had a basal-cell carcinoma of the skin.

Nodular Hyperplasia of Prostate.—This lesion was significant in six patients, three of whom showed hypertrophy of the urinary bladder. Three had undergone operation five weeks to several years previously—two, perineal resection and one, suprapubic resection. Three showed cystitis, summarized under "Infection," above.

Operative Complications.—Among seven patients, five men and two women, with three carcinomas of the large intestine, two of the stomach, one of a lung, and one of the thyroid gland, who had undergone three resections, two colostomies, and two exploratory laparotomies 1 day to 13 months previously, nine operative complications occurred, as follows: bronchopneumonia, in 2; embolism of the lungs, in 2; acute ulcerative esophagitis, in 2, and bacteremia, hemoperitoneum (500 cc.), and strangulation of the ileum with gangrene, in 1 each.

In the two cases of embolism of the lungs, the emboli were large and associated with an infarct of a lung in one case.

Accidents.—Among five patients, four men and one woman, six accidents were noted. Three occurred in the hospital, the first being aspiration of gastric contents into the lungs, the second an x-irradiation fistula between skin and larynx, and the third a fracture of the neck of the left femur sustained 69 and 48 days, respectively, after closed and open reductions. Two were related to fractures of the humerus and of the neck of the left femur, the latter occurring 18 days after open reduction and both being radiographically consistent with pathologic fracture due to metastases of prostatic carcinoma. One was an organized subdural hematoma over the right frontoparietal region of the brain two years after craniotomy.

Urinary Tract Lesions.—Among three patients, two men and one woman, nephrosis was noted in two and a calculus of the urinary bladder in one.

Miscellaneous Lesions.—Among five patients, three men and two women, the following five miscellaneous lesions were found: amyloidosis of adrenals and kidneys, atrophy of the cortex of the adrenal glands, atrophy of the brain, weight 1,010 gm.; calculi of the prostate, and metastatic squamous-cell carcinoma in the brain from the primary site on the skin of the face.

Brain Examination.—The brain was not examined in 45 cases, was examined and found negative in 8 cases, and was examined in 5 cases, the findings being an organized subdural hematoma and recent infarct, atrophy of the brain, metastatic carcinoma, an arachnoid cyst, and a recent infarct, in one each, as noted in preceding sections.

Summary of Fifty-Eight Cases of Cancer.—In this series of cancer cases in 58 persons 80 years of age and older, about 1 out of 3 was a man. With 1 man having 2 primary cancers of significance, the total of 59 cancers was distributed as follows: prostate, 16; stomach, 7; large intestine, 6; skin, 5; hematopoietic system, 4; lungs, 4; pancreas, 4; breasts, 3; pharynx, 3; and cystic duct, urinary bladder, jejunum, larynx, liver, palate, and thyroid gland, 1 each. The 59 cancers included 55 carcinomas, 2 lymphocytic lymphasarcomas, 1 plasma-cell myeloma, and 1 case of myelogenous leukemia. Inflammatory lesions contributing to death were moderate to severe bronchopneumonia, in 14 cases; cystitis, in 14 cases, and pyelonephritis, in 8 cases. Cardiovascular lesions of auxiliary lethal significance were embolism of the lungs, in 11 cases; arteriosclerosis of the coronary, cerebral, or popliteal arteries, in 10 cases, and essential hypertension, in 3 cases. Other ancillary anatomic features were abscesses, esophagitis, lobar pneumonia, enteritis, acute central necrosis of the liver, chronic peptic ulcer, gangrene of the large intestine, nodular hyperplasia of the prostate, and fractures. Operative complications included bronchopneumonia, pulmonary embolism, esophagitis, and bacteremia.

C. Infection

Sex and Age.—Of 44 persons dying of infection, 35 were men and 9 were women,

a ratio of 3.9; 38 were 80 to 89 years of age, and 6 were 90 years of age and older.

Site.—The sites of the infection in this series were as follows: lungs, in 38, and liver, meninges, middle ear, pericardium, tooth socket, and upper extremity, in 1 each. Of the cases of lung infections, both lungs were involved in 28, the right in 4, and the left in 6 (upper lobe, 1, and lower lobe, 5).

Type.—The type of infection was bronchopneumonia (Zeman and Wallach, 1946[36]) in 31; tuberculosis of the lungs, in 5; chronic abscess of the lungs, in 2, and acute cellulitis of an upper extremity, acute otitis media, acute suppurative meningitis, chronic abscess of a molar tooth socket, infectious hepatitis, and tuberculosis of pericardium, in 1 each. Of the 31 cases of bronchopneumonia, 27 were acute pyogenic, with partial organization in 3; 3 were chronic suppurative, and 1 was viral. Of the six cases of tuberculosis, the lungs were principally involved in five and the pericardium in one. The five cases of pulmonary tuberculosis included nodular; nodular and miliary; nodular, miliary, and cavitative; miliary, and nodular and cavitative, one case each.

Other Infection.—Among 20 patients, 16 men and 4 women, the 25 other inflammatory lesions were distributed as follows: cystitis, 15 (chronic, 14; subacute, 1); acute ulcerative esophagitis, 3; acute suppurative prostatitis, 2, and aspirative bronchopneumonia, pyogenic bronchopneumonia complicating tuberculosis of the lungs, acute ulcerative colitis, acute ulcerative duodenitis, and acute ulcerative pyelitis, 1 each.

Cardiovascular Lesions.—Among 25 patients, 19 men and 6 women, 37 cardiovascular lesions were found.

Embolism of the lungs was observed in seven, in five of which the embolus was large and in two small; two patients had recent infarcts of the lungs, and three showed thrombosis of veins—left common iliac, adrenal, and prostatic, one each.

Dilatation of the heart was seen in six cases.

Arteriosclerotic stenosis of the coronary arteries was found in four cases, with small old infarcts of the left ventricle of the heart in three, and fibrosis of the myocardium of the left ventricle in one; three showed dilatation of the heart.

Hypertrophy of the heart, weight 410 to 670 gm., was noted in six cases.

Three cases showed minimal to moderate amyloidosis of the heart; two, arteriosclerotic mural thrombosis of the aorta; two, arteriosclerotic stenosis of cerebral arteries with recent infarcts of the brain, and two, bone-marrow embolism of the lungs.

Single examples of the following lesions were recorded: arteriolosclerosis of the kidneys, mural thrombosis of the mitral valve of the heart, mural thrombosis of the aortic valve of the heart, and rheumatic stenosis of the mitral valve of the heart.

In one patient dying of meningococcic meningitis essential hypertension was manifested by arteriosclerotic stenosis of the coronary arteries, an old infarct of the left ventricle of the heart, hypertrophy of the heart (weight 650 gm.), dilatation of the heart, edema of the lungs, and hydropericardium.

Alimentary Tract Lesions.—Among 29 patients, 21 men and 8 women, 42 alimentary tract lesions were distributed as follows: atrophy of the liver (weight 710 to 1,010 gm.), 10; diverticula of the intestine, 8; calculi of the gallbladder, 7; fatty metamorphosis of the liver, 4; chronic cholecystitis, 3; acute central necrosis of the liver, 2; acute passive hyperemia of the liver, 2; incarceration of the ileum, 2, and calculi of the common bile duct, chronic ulcer of the stomach, hyalinization of the islets of the pancreas, and melanosis of the large intestine and appendix, 1 each.

The eight examples of diverticula of the intestine were distributed as follows: large intestine, four; ileum (Meckel's), two; duodenum, one, and appendix, one.

Of the seven cases of cholelithiasis, three showed pigment calculi.

All three cases of chronic cholecystitis showed calculi, two pigment.

The first case of incarceration of the ileum was bland within an inguinal hernia sac; the second case was complicated by early gangrene, related to fibrous peritonitis.

Benign Tumors.—Among 7 men and 2 women, 10 benign tumors included three leiomyomas (stomach, 2, and jejunum, 1), three cysts (kidneys, 2, and esophagus, 1), and cortical adenoma of the adrenal, chromophobic adenoma of the pituitary, lipoma of the ileum, and polyp of the endometrium, 1 each.

Nonlethal Cancers.—All eight patients were men, with four carcinomas of the prostate, a small infiltrative carcinoma of the urinary bladder, a squamous-cell carcinoma of the penis, a lymphocytic lymphosarcoma of the hematopoietic system, and a liposarcoma of the retroperitoneum.

Nodular Hyperplasia of Prostate.—This lesion was significant in 13 patients, 11 of whom showed hypertrophy, 1 a diverticulum, and 1 calculi of the urinary bladder. Of the 13, 3 had undergone operation one to four years previously—transurethral resection, suprapubic resection, and cystostomy, 1 each.

Miscellaneous Lesions.—Among 25 patients, 20 men and 5 women, 41 miscellaneous lesions included operative absence of organs, 7; accidental injuries, 5; obliterative fibrous pleuritis, 5 (bilateral, 3; right-sided, 2), and hydronephrosis, 3 (bilateral, 2; right-sided, 1). Decubital ulcers of the skin, bilateral hydrothorax, hypoplasia of the bone marrow, lipid pneumonia, and osteoporosis were noted in two cases each. One example of each of the following lesions was observed: acute necrosis of adrenal cortex, anthracosis of lungs, aspiration of gastric contents into the lungs, atrophy of the brain, weight 1,000 gm., calcification of renal pyramids, diverticula of the urinary bladder, emaciation, weight 34 kg., horseshoe kidney, hypertrophy of urinary bladder, dorsal kyphosis, and nodular goiter, weight 300 gm.

Of the seven instances of surgical removal of organs, the appendix was absent in 4, the gallbladder in 3, the uterus in 2, a testis in 1, and the Fallopian tubes in 1.

Of the five patients with accidents three sustained their injuries in the home and two in the hospital. The types of lesions received in the accidents were fracture of the neck of a femur, in 2; subdural hematoma, in 2, and gunshot wound, in 1.

General Related Lesions.—Among 14 patients, 13 men and 1 woman, 22 lesions related to infection were easily summarized as follows: pleuritis, 5 (acute fibrinous, 3; obliterative fibrous, 2); tuberculosis of various sites, 4 (anus, bronchial lymph nodes, hematopoietic system and adrenals, spleen and kidneys, 1 each); significant hydrothorax, 2 (bilateral, 1; left-sided, 1); chronic passive hyperemia of the liver, 2, and acute abscesses of the upper lobe of the right lung, acute lymphadenitis of bronchial lymph nodes, atelectasis of the upper lobe of the left lung, dilatation of the heart, emphysema of the opposite lung, chronic empyema of the left pleural cavity, myeloid hyperplasia of bone marrow, chronic suppurative osteomyelitis of the mandible, and cutaneous sinus, 1 each.

Special Related Lesions.—In 13 cases, 5 of bronchopneumonia, 3 of tuberculosis, and 5 of a variety of infections, related lesions will be summarized.

CASE 1.—Man, 80. Bronchopneumonia, pyogenic, organized, lungs; chronic empyema, left pleural cavity; fistula, descending thoracic segment of aorta and bronchus of lower lobe of left lung; massive hemorrhage of lungs; edema of lungs.

CASE 2.—Man, 83. Bronchopneumonia, pyogenic, necrotizing, lungs; bacteremia; acute necrotizing pyelonephritis; general exfoliative dermatitis; myeloid hyperplasia of bone marrow.

CASE 3.—Man, 90. Bronchopneumonia, pyogenic, lungs; left hydrothorax (1,000 cc.); right obliterative pleuritis; dilatation of heart, and acute passive hyperemia of liver.

CASE 4.—Man, 85. Bronchopneumonia, pyogenic, lungs; hypertrophy of heart, weight 430 gm.; dilatation of heart; edema of lungs.

CASE 5.—Man, 82. Bronchopneumonia, pyogenic, chronic suppurative, upper lobe, left lung; obliterative fibrous pericarditis; hypertrophy of heart, 490 gm.; fibrosis of myocardium of left ventricle; edema of lungs; myeloid hyperplasia of bone marrow.

CASE 6.—Woman, 84. Tuberculosis, pericardium; tuberculosis of mediastinal lymph nodes; fibrosis of left ventricle of heart; mural thrombosis of left ventricle of heart; hypertrophy of heart, weight 500 gm.; dilatation of heart; left obliterative fibrous pleuritis; right hydrothorax (1,500 cc. of fluid); acute passive hyperemia of liver.

CASE 7.—Man, 87. Tuberculosis, miliary, nodular, and cavitative, lungs; arteriosclerotic thrombosis of pulmonary arteries; right-sided hypertrophy of heart (thickness right ventricle 5 mm.; weight 340 gm.); right obliterative fibrous pleuritis, and chronic myocarditis.

CASE 8.—Man, 81. Tuberculosis, nodular and cavitative, lungs; right-sided hypertrophy of heart (thickness right ventricle 7 mm.; weight 310 gm.); edema of lungs.

CASE 9.—Man, 88. Acute cellulitis, left upper extremity; clinical septicemia; partial collapse of left lung; focally organized bronchopneumonia; right obliterative fibrous pleuritis.

CASE 10.—Man, 90. Acute otitis media, left; acute purulent meningitis; edema of lungs.

CASE 11.—Woman, 93. Acute suppurative meningitis (Neisseria meningitidis); meningococcemia; acute dermatitis.

CASE 12.—Man, 80. Chronic abscess, pyogenic, upper lobe, left lung; chronic empyema of left pleural cavity; dilatation of heart; edema of lungs; right hydrothorax (500 cc. fluid).

CASE 13.—Man, 84. Infectious hepatitis; atrophy of liver, weight 980 gm.; acute hemorrhagic pancreatitis; hepatocellular jaundice; ascites, 1,000 cc. fluid; hydrothorax (right, 1,000 cc.; left, 1,000 cc. fluid).

Brain Examination.—The brain was not examined in 26 cases, was examined and found negative in 11 cases, and was examined in 7 cases, of which 2 showed meningitis, 2 subdural hematomas, 2 recent infarcts, and 1 atrophy as listed above.

Summary of Forty-Four Cases of Infection.—In 44 cases of infection in persons 80 years of age or older, about 10 out of 11 were men; in 38 the infection involved the lungs, in 28 both lungs, in 4 the right lung and in 6 the left lung. The 31 cases of bronchopneumonia were subdivided into 27 cases of acute pyogenic, 3 cases of chronic suppurative, and 1 case of viral type; the 5 cases of tuberculosis of the lungs showed variable features, and 2 chronic abscesses accounted for the remainder of the lung lesions. Significant contributory causes of death in the 44 cases included thrombotic embolism of the lungs, 7 cases; arteriosclerotic stenosis of coronary arteries with cardiac infarction, 3 cases; cerebral infarction, 2 cases; rheumatic stenosis of the mitral valve, 1 case, and essential hypertension, 1 case. Other lesions, such as esophagitis, acute central necrosis of the liver, gangrene of the ileum, acute necrosis of adrenal cortex, and subdural hematoma, were auxiliary lethal factors.

D. Accident

Sex and Age.—Of 43 persons dying of injuries sustained in an accident, 19 were men and 24 were women, or a ratio of 0.80; 37 were 80 to 89 years of age, and 6 were 90 years of age and older.

Locale.—The locale of the accidents was as follows: home, 37; hospital, 3; street, 2, and motor vehicle, 1.

Type of Injury.—The major lesions were as follows: fracture, in 36 cases (Oltman and Friedman, 1953[23]); burns, in 3 cases, and suicide by gunshot, subdural hematoma, operative trauma to a ureter, and asphyxia by food, in 1 case each.

Fractures.—The fractures were divided according to site, as follows: femur, 31; humerus and ribs, 2; ribs, vertebrae, and clavicle, 1; ilium, 1, and patella, 1. The right femur was involved in 15 cases; the left, in 16 cases. The site of the fracture of the femur was between the trochanters in 19 cases, through the neck in 11 cases, and through the distal third of the shaft in 1 case. Of the 31 patients, 14 were treated by closed reduction and traction, and 17 (6 fractures through the neck and 11 between the trochanters) were treated by open reduction and nailing. The patients of the latter group survived operation for 8 hours to 46 days.

Other Accidents.—The seven cases sustaining such accidents were as follows:

CASE 1.—Woman, 81. Home accident; burns, second and third degree, face, trunk, and right upper extremity.

CASE 2.—Woman, 84. Home accident; burns, second and third degree, right hand, sacrum, thighs, and legs.

CASE 3.—Man, 84. Home accident; burns, second and third degree, left flank, right thigh, and right knee; nephrosis, lower-nephron type.

CASE 4.—Man, 86. Home accident; suicide, gunshot wound, left thoracic region, left 6th to 10th intercostal spaces; left hemothorax, 1,700 cc.; laceration, left lung; hemorrhage, left lung.

CASE 5.—Man, 83. Home accident; subdural hematoma, diffuse, brain.

CASE 6.—Man, 82. Hospital accident; herniorrhaphy scar, left inguinal scar recent; absence, left testis; wound, left ureter; hydroureter, left; hydronephrosis, left; acute pyelonephritis, left; perinephric abscess, left.

CASE 7.—Man, 80. Hospital accident; aspiration, food, larynx, trachea, bronchi; asphyxia, clinical.

Infection.—Among 34 patients, 14 men and 20 women, 46 inflammatory lesions were distributed as follows: moderate to severe bronchopneumonia, 13 (aspiration, 1); cystitis, 11 (chronic, 10; subacute, 1); early bronchopneumonia, 10 (aspiration, 1; organized, 1); acute ulcerative esophagitis, 6; acute ulcerative colitis, 2; acute ulcerative enteritis, 1; acute ulcerative laryngitis, 1, and both chronic suppurative cellulitis and osteomyelitis, 1.

Embolism of Lungs.—Among 15 cases, 10 men and 5 women, embolism of the lungs was large in 4, medium in 6, and small in 5; 4 cases showed recent pulmonary infarcts; thrombosis of the right atrium of the heart occurred in 2 cases, and thrombosis of veins was seen in 4—internal iliac, external iliac, common iliac, and inferior vena cava. Fat embolism of the lungs (Warren, 1946[34]), as proved by fat stains in five patients, three women and two men, was probably much more frequent, but was not checked for routinely, as is desirable in all cases of fractures and burns.

Essential Hypertension.—Seven patients, two men and five women, had anatomic findings consistent with essential hypertension, a contributory cause of death in four. The heart weighed 330 to 390 gm. in three women (body weight, 38 to 48 kg.) and 430 to 550 gm. in two men and two women. Arteriolosclerosis of the kidneys was observed in six patients; dilatation of the heart, in four; edema of the lungs, in three; arteriosclerotic stenosis of coronary arteries, in two; acute passive hyperemia of the liver, in two, and infarcts of the myocardium of the left ventricle, fibrosis of the myocardium of the left ventricle, hydrothorax, recent infarct of the spleen, and chronic passive hyperemia of the liver, in one each.

Arteriosclerosis of Coronary Arteries.—Four patients, two men and two women, had arteriosclerosis of the coronary arteries, a contributing cause of death in two. Three showed stenosis of coronary arteries; one showed thrombosis of a coronary artery. The myocardium of the left ventricle revealed old infarcts in two, a recent infarct in one, and fibrosis in one.

Other Cardiovascular Lesions.—Among 23 patients, 10 men and 13 women, 31 lesions were distributed as follows: edema of the lungs, 5; arteriolosclerosis of the kidneys, 3; acute passive hyperemia of the liver, 3; hypertrophy of the heart, weight 420 to 465 gm., 3; patent foramen ovale, 3; infarcts of the brain, 2; recent infarcts of the spleen, 2; arteriosclerotic mural thrombosis of the aorta, 2; mural thrombosis of the aortic valve, 2, and arteritis nodosa, atrophy of the heart (weight 200 gm.), calcific stenosis of the aortic valve, dilatation of the heart, chronic rheumatic endocarditis, and recent infarct of the kidney, 1 each.

Recent infarcts of the right kidney and right adrenal complicated one case of arteriosclerotic mural thrombosis of the aorta. An infarct of the right temporal lobe of the brain was old. An infarct of the midbrain and pituitary gland was recent. The 89-year-old woman with arteritis nodosa received large doses of sulfonamide. The 81-year-old woman with chronic rheumatic endocarditis had stenosis of the mitral valve and hypertrophy of the heart, weight 470 gm. The 86-year-old man with calcific aortic stenosis had hypertrophy of the heart, weight 435 gm., and edema of the lungs.

Alimentary Tract Lesions.—Among 34 patients, 11 men and 23 women, 46 alimentary tract lesions occurred as follows: atrophy of the liver, weight 730 to 1,000 gm.,

11 cases; cholecystitis, 10; diverticula of the intestine, 9; calculi of the gallbladder, 6; fatty metamorphosis of the liver, 4, and portal cirrhosis of the liver, diverticulum of the middle third of the esophagus, fat necrosis of the pancreas, postmortem perforation of the stomach, chronic ulcer of the duodenum, volvulus of the ileum and cecum with gangrene of the cecum, 1 each.

The cholecystitis in eight women and two men was chronic in nine and acute diffuse in one. Calculi were noted in eight; seven were multiple (four pigment) and one was solitary. Hydrops (150 and 500 cc., respectively), was observed in two cases.

The nine instances of diverticula of the intestine occurred in seven women and one man, with one woman showing two diverticula in the duodenum and many in the sigmoid segment of the large intestine. The diverticula, multiple in seven and solitary (Meckel's) in two, were distributed in the large intestine in five cases, in the jejunum in two cases, in the duodenum in one case, and in the ileum in one case.

In the six patients with calculi of the gallbladder, five women and one man, the calculi were multiple in all six and of pigment type in one.

Benign Tumors.—Among 12 women and 1 man, 16 benign tumors included 6 leiomyomas of the uterus, 3 polyps of the endometrium, and 1 each of the following: cyst of the thyroid gland, hamartoma of a lung, leiomyoma of the stomach, carcinoid tumor of the ileum, polyp of the large intestine, cystadenoma of a kidney, and serous cystadenomas of the ovaries.

Nonlethal Cancers.—Of five patients, four men and one woman, incidental carcinomas involved the prostate in three, the large intestine in one, and the skin in one.

Nodular Hyperplasia of Prostate.—This lesion was significant in eight patients, six of whom showed hypertrophy of the urinary bladder, one, an infarct of the prostate, and one, diverticula of the urinary bladder.

Operative Absence of Organs.—In four patients, parts of the body had been surgically absent for many years, two with amputation of a right upper extremity and one with a left eye removed because of trauma. The fourth patient had elective removal of tubes and ovaries.

Miscellaneous Lesions.—Among 21 patients, 9 men and 12 women, the following 27 lesions were found: decubital ulcers of the skin, in 10 cases; atrophy of the brain, weight 980 and 1,085 gm., in 2 cases; clinical or gross fat embolism, in 2 cases; lacerations and hemorrhages of the skin, in 2 cases; obesity, weights 80.0 and 83.5 kg., in 2 cases, and old healed intertrochanteric fracture of the right (opposite) femur sustained at home, aspiration of gastric content into the lungs, atrophy of the kidneys (weights 80 and 60 gm.), atrophy of the left testis, clinical dermatitis herpetiformis, nodular goiter (70 gm.), bilateral obliterative fibrous pleuritis, clinical morphine poisoning, and septicemia, in 1 case each.

Brain Examination.—The brain was not examined in 25 cases, was examined and found to be negative in 11 cases, and was examined in 7 cases, 4 of which showed infarcts, 2 atrophy, and 1 a subdural hematoma, as listed above.

Summary of Forty-Three Accidents.—In this series of 43 accidents in persons 80 years of age and older, about 4 patients out of 7 were women; 37 occurred at home; 30 fractures were noted between the trochanters or through the neck of the femur. Six other cases of fracture, three of burns, and one each of suicide, subdural hematoma, operative trauma to a ureter, and asphyxia by food were observed. Significant contributory causes of death included thrombotic embolism of the lungs, in 15 cases; bronchopneumonia, in 14; fat embolism of lungs, in 5; essential hypertension, in 4; arteriosclerotic stenosis of coronary arteries with cardiac infarction, in 2; cerebral infarction, in 2, and rheumatic stenosis of the mitral valve, arteritis nodosa, and calcific stenosis of the aortic valve, in 1 each. Other lesions, such as esophagitis, enteritis, colitis,

osteomyelitis, volvulus of the ileum and gangrenous cecum, and portal cirrhosis of the liver, were less common auxiliary lethal factors.

E. Nodular Hyperplasia of Prostate

Age.—Of the 29 men with this lesion as the principal cause of death, 24 were 80 to 89 and 5 were 90 to 99 years of age.

Features in Prostate.—Nodular hyperplasia (Moore, 1943 [19]) involved mainly the lateral lobes in 28 cases and the middle lobe in 1 case. Infarcts of the hyperplastic tissue were noted in four cases and calculi of the prostate in one. Six cases showed clinical uremia.

Operations.—In 13 cases with operations designed to relieve prostatic obstruction (Young, 1943 [35]), 11 resections of various types were done—transurethral in 7, perineal in 2, suprapubic in 1, and retropubic in 1. Five patients had one resection and three had two resections. Three resections were done 1 to 25 years before death; 8 were performed 3 to 70 days before death. One perineal resection was complicated by a urethrorectal fistula. The retropubic resection was complicated by cutaneous wound cellulitis. Seven patients had cystostomy—the only operation in five and coupled with resection in two.

Hypertrophy and Urinary Bladder.—In 25 cases hypertrophy of the urinary bladder accompanied the nodular hyperplasia of the prostate; 3 of these had diverticula, multiple in 2 and solitary in 1.

Hydroureter and Hydronephrosis.—Both these lesions were observed in five cases, being bilateral in four and right-sided in one.

Infection.—Among 27 cases, 77 inflammatory lesions involved the urinary or genital tracts and other sites.

Cystitis (Karsner, 1949 [15]) occurred in 24 cases, being chronic in 20, subacute in 2, acute in 1, and chronic suppurative in 1. Pyelonephritis (Bell, 1950 [4]), occurring in 11 cases, was chronic suppurative in 6, acute in 2, acute suppurative in 1, chronic in 1, and subacute in 1, and was bilateral in 9, right-sided in 1, and left-sided in 1. Chronic pyelitis was found in three cases, and chronic ureteritis, in one.

Prostatitis, occurring in four cases, was acute in two and acute suppurative in two. Acute suppurative epididymitis and chronic suppurative seminal vesiculitis were noted in one case each.

Moderate to severe bronchopneumonia, present in 12 cases, was bilateral in 7, right-sided in 4, and left-sided in 1. Early bronchopneumonia was noted in four cases; acute ulcerative esophagitis, in 4; bacteremia, in 2, and acute ulcerative duodenitis, in 2. Single examples of the following were noted: acute abscesses of the lower lobe of the right lung, acute enteritis, acute gastritis, chronic osteomyelitis of thoracic vertebrae with paravertebral abscess, acute fibrinous pericarditis, early lipid pneumonia, chronic suppurative synovitis of the right shoulder joint, and nodular tuberculosis of the right adrenal gland, associated with tuberculosis of a bronchial lymph node.

Embolism of Lungs.—Nine patients showed embolism of the lungs, three with large, three with medium, and three with small emboli. Recent pulmonary infarcts occurred in three cases. The emboli were septic in two cases. The sources of these emboli were not determined.

Cardiovascular Lesions.—Among 22 cases, 31 cardiovascular lesions included hypertrophy of the heart, weight 450 to 550 gm., with other lesions in 6. These lesions were edema of the lungs, in five; dilatation of the heart, in four; fibrosis of the myocardium of the left ventricle, in three; passive hyperemia of the liver, in two, and arteriolosclerosis of the kidneys, cardiac cirrhosis of the liver, bilateral hydrothorax, clinical shock, and mural thrombosis of the left atrium of the heart, in one each.

Also observed were dilatation of the heart, in five cases; acute passive hyperemia of the liver, in three cases; hypertrophy of the heart (weight 430 to 500 gm.) without other lesions, in three cases; arteriolosclerosis of the kidneys, in two cases; arterioscle-

rotic mural thrombosis of the aorta, in two cases, and edema of the lungs, in two cases. Single instances of the following were noted: minimal amyloidosis of the heart, atrophy of the heart (weight 135 gm.), fibrosis of the myocardium of the left ventricle, mural thrombosis of the right atrium of the heart, and acute necrotizing thrombosis of the right gastroepiploic artery with hemorrhage into the jejunum.

Three cases of arteriosclerosis follow:

CASE 1.—Man, 83. Arteriosclerotic stenosis, anterior descending branch, left coronary artery; old infarct, left ventricle, heart.

CASE 2.—Man, 82. Arteriosclerotic thrombosis, organized, anterior descending branch, left coronary artery; fibrosis, myocardium, left ventricle; hypertrophy, heart, weight 460 gm.; dilatation of heart.

CASE 3.—Man, 93. Arteriosclerotic thrombosis, right femoral artery, clinical; gangrene, right knee, leg, and foot.

Alimentary Tract Lesions.—Among 20 cases, 28 lesions included atrophy of the liver (weight 820 to 995 gm.), in 5; calculi of the gallbladder, in 5; diverticula, in 4; chronic cholecystitis, in 3; fat necrosis of the pancreas, in 3, and a 1 cm. calculus of the head of the pancreas, acute cholescystitis with pigment calculi of the gallbladder, portal cirrhosis of the liver with ascites (2,000 cc. of fluid), hyalinization of the pancreatic islets, intestinal-cell metaplasia of the mucosa of the stomach, acute central necrosis of the liver, a 15 mm. chronic ulcer of the antrum of the stomach, and a 3 cm. chronic ulcer of the duodenum, in 1 each.

Of the five cases of cholelithiasis, three showed pigment calculi. All three cases of chronic cholecystitis showed calculi, one of pigment type; one patient had had recent cholecystectomy.

The four cases of diverticula included three of solitary lesions, located as follows: in the esophagus (resected successfully 44 months before death), in the duodenum, and in the ileum (Meckel's), and one multiple lesion of the descending and sigmoid segments of the large intestine.

Benign Tumors.—Five benign tumors comprised a 25 mm. adenoma of the cortex of the right adrenal, a 7 cm. cyst of the left kidney, a 1 cm. cystadenoma of the right kidney, a 3 mm. and a 20 mm. papilloma of the urinary bladder, and a 1 cm. polyp of the sigmoid segment of the large intestine.

Nonlethal Cancers.—The two nonlethal cancers were occult carcinomas of the prostate.

Miscellaneous Lesions.—In 19 cases, 30 assorted lesions included atrophy of the testes, in 3 (unilateral in 2 and bilateral in 1; hydrothorax (400 to 1,000 cc. of fluid), in 3 (left-sided in 2 and bilateral in 1); right-sided obliterative fibrous pleuritis, in 3; calculi of the urinary bladder, in 2; decubital ulcers, in 2; hospital accidents, in 2, and minimal or moderate silicosis of lungs and bronchial lymph nodes, in 2.

One hospital accident was a fracture of the neck of the right femur, treated by open reduction 18 days before death. The other hospital accident was related to lacerations of the urinary bladder, with vesical hemorrhage of 200 cc. and hemoperitoneum (400 cc.), sustained during a transurethral resection of the prostate.

Single examples of the following lesions were found: absence of the right testis, minimal amyloidosis of the spleen, aplasia of the left testis and seminal vesicle, ascites (500 cc. fluid), clinical diabetes mellitus, nodular goiter (weight 102 gm.), horseshoe kidney with calculi of the left pelvis, right inguinal hernia, myeloid hyperplasia of the bone marrow, hyperplasia of the interstitial cells of the testes, hyperplasia of a parathyroid gland, lymphocytic leukemoid reaction of the hematopoietic system, and a tracheostomy wound.

Brain Examination.—The brain was not examined in 22 cases, was examined and found negative in 6, and showed subarachnoid hemorrhage over the left temporal lobe in 1.

Summary of Twenty-Nine Cases of Nodular Hyperplasia of Prostate.—Of the 29 men 80 years of age and older with this lesion as the principal cause of death, the

lateral lobes of the prostate were mainly involved in 28. Eight patients had resection of the hyperplastic tissue to relieve obstruction; five had cystostomy only. Hypertrophy of the urinary bladder was significant in 25 cases. Hydroureter and hydronephrosis were present in only five cases. Cystitis, present in 24 cases, was chronic in 20. Pyelonephritis was bilateral in nine cases and chronic suppurative in six. Moderate to severe bronchopneumonia contributed to death in 12 cases. Other inflammatory lesions, such as esophagitis, bacteremia, duodenitis, lung abscess, osteomyelitis, synovitis, and tuberculosis, were less important contributing factors. Embolism of the lungs was an auxiliary fatal lesion in nine cases. Other lesions of variable lethal significance were hypertrophy of the heart with cardiac failure, arteriosclerosis of coronary or lower-extremity arteries and sequelae, portal cirrhosis of the liver, acute central necrosis of the liver, chronic peptic ulcer, and hospital accidents.

F. Alimentary Tract Diseases

Sex and Age.—Of 20 persons dying of alimentary tract diseases, 14 were men and 6 were women; all were 80 to 89 years of age.

Type of Cases.—Of these 20 patients, peptic ulcer was found in 9, cholecystitis in 4, appendicitis in 2, starvation in 2, adhesion of the peritoneum in 1, hernia in 1, and stricture of esophagus in 1.

Peptic Ulcer

Of nine cases of chronic peptic ulcer (Boles and Dunbar, 1946 [8]), in six men and three women, seven occurred in the duodenum and two in the stomach. The seven duodenal ulcers were 10 to 30 mm. in diameter (five cases with dimensions available); five were single, and two were double. One patient had a recent colostomy for unsubstantiated intestinal obstruction. The two gastric lesions were 15 and 25 mm., respectively, in diameter. One patient had recent subtotal gastrectomy and gastroenterostomy. The complications of these nine peptic ulcers were as follows: erosion of an artery and gastrointestinal hemorrhage, in six; perforation (recently repaired) and acute fibrinopurulent peritonitis, in two, and fibrous stenosis of the duodenum related to a chronic duodenal ulcer perforated and repaired 10 years before death, in one.

Cholecystitis

The features related to the four cases of cholecystitis (Andrews, 1935 [1]) are summarized as follows:

Case 1.—Woman, 86. Chronic suppurative cholecystitis, one week after cholecystectomy; hydrops, gallbladder; calculi, gallbladder.

Case 2.—Man, 80. Chronic cholecystitis, two weeks after cholecystectomy; calculi, gallbladder; calculus, right hepatic duct.

Case 3.—Man, 82. Acute suppurative cholecystitis; empyema, gallbladder; calculi, gallbladder; calculus, 8 mm., common bile duct; acute suppurative choledochitis; acute focal necrosis, liver; acute focal suppurative pancreatitis.

Case 4.—Woman, 84. Chronic cholecystitis, 37 years after cholecystectomy; probable calculi of gallbladder; ventral hernia, 31 years; incarceration of duodenum, ileum, and cecum, in ventral hernia sac; acute ulcerative enteritis; hemorrhage, stomach and intestine.

Appendicitis

The features related to the two cases of appendicitis (Stalker, 1940 [30]) were as follows:

Case 1.—Man, 83. Acute, diffuse, suppurative, gangrenous appendicitis, several months after appendectomy; abscess, 1,000 cc., right upper quadrant, peritoneal cavity.

Case 2.—Man, 81. Acute gangrenous appendicitis, one month after appendectomy.

Bronchopneumonia contributed to death in both these cases.

Starvation

This condition was illustrated in the first patient by severe wasting of the body tissues and was accompanied in the second patient by severe hypoproteinemia and anasarca.

Case 1.—Man, 89, weight 33.6 kg., height 180 cm. Edema, lungs; atrophy of liver, weight 550 gm.; hemosiderosis, spleen; chronic ulcerative esophagitis; hiatus hernia, esophagus; herniation, cardia, stomach.

Case 2.—Man, 85, weight 80 kg. (much fluid), height 177 cm. Hypoproteinemia, clinical, albumin 1.82 gm. % and globulin 2.09 gm. %; hypertrophy,

heart, 450 gm.; dilatation, heart; edema, lungs; hydrothorax (right side, 500 cc.; left side, 600 cc.); ascites, 1,500 cc. of fluid; anasarca; serous atrophy, body adipose tissue; bilirubin pigmentation, liver; hemosiderosis, bone marrow; atrophy, testes.

Adhesion of Peritoneum

Woman, 84. Adhesion, omental, peritoneum, many years after hysterectomy and two days following exploratory laparotomy; incarceration, jejunum, omental adhesions; early gangrene, jejunum; acute fibrinopurulent peritonitis.

Hernia

Man, 89. Bilateral inguinal hernia; incarceration, small intestine, right inguinal hernia; early gangrene, small intestine.

Stricture of Esophagus

Man, 83. Stricture of lower end of esophagus, etiology not established; recent jejunostomy; acute jejunitis; recent tracheostomy. Bronchopneumonia contributed to the death of this patient.

Other Alimentary Tract Lesions.—Among 13 patients, 8 men and 5 women, 21 other lesions of the alimentary tract were as follows: diverticula of the intestine, in 5; atrophy of the liver, weight 900 to 1,000 gm., in 4; calculi of the gallbladder, in 4; cholecystitis, in 2, and calculi of the pancreatic ducts with atrophy of the pancreas, fatty metamorphosis of the liver, right inguinal hernia, melanosis coli, acute central necrosis of the liver, and fat necrosis of the pancreas, in 1 each.

The intestinal diverticula were multiple and in the large intestine in four cases and solitary and in the duodenum in one. The calculi of the gallbladder were multiple, pigment in two cases, and solitary in two cases. The first case of cholecystitis was chronic and without calculi; the second case, chronic suppurative with a 14 mm. calculus, involved a gallbladder partly surgically removed many years before.

Infection.—Among 13 patients, 11 men and 2 women, 22 inflammatory lesions included moderate to severe bronchopneumonia, 4; chronic cystitis, 4; acute or chronic ulcerative esophagitis, 3; early bronchopneumonia, 2; acute ulcerative gastritis, 2; and abscesses of the right lung, acute bronchitis, acute duodenitis, acute epididymitis, acute fibrinous pericarditis, acute prostatitis, and chronic right pyelonephritis, 1 each.

Cardiovascular Lesions.—Among 11 patients, 9 men and 2 women, 16 cardiovascular lesions included essential hypertension and other lesions, 4. These lesions were hypertrophy of the heart, weight 430 to 600 gm., four; arteriosclerotic stenosis of the coronary arteries, two; dilatation of the heart, two; edema of the lungs, two; old infarcts of the left ventricle of the heart, one, and fibrosis of the myocardium of the left ventricle, one.

Also noted were amyloidosis of the heart, in two cases; thrombosed arteriosclerotic aneurysm of the abdominal segment of the aorta, two; dilatation of the heart, two, and arteriosclerotic mural thrombosis of the aorta, arteriosclerotic thrombosis of the common iliac arteries, edema of the lungs, rheumatic endocarditis and myocarditis, hemorrhage of the lungs, and acute passive hyperemia of the liver, in one each. In one patient, amyloidosis of the heart was complicated by edema of the lungs, bilateral hydrothorax (200 to 500 cc. each), acute passive hyperemia of the liver, and a 2 cm. recent infarct of the spleen.

Benign Tumors.—Among three men and three women, seven benign tumors were as follows: three cysts, two serous of the ovaries and one of the right kidney; two polyps, one of the endometrium and one of the large intestine; a 1 cm. cystadenoma of the right kidney, and a 15 mm. papilloma of the urinary bladder.

Nonlethal Cancers.—No incidental cancer was found among these 20 patients.

Nodular Hyperplasia of Prostate.—This lesion was significant in six patients, two of whom showed hypertrophy of the urinary bladder, two, a single diverticulum of the urinary bladder, and one, a recent infarct of the prostate. One patient had had suprapubic resection several years before death.

Miscellaneous Lesions.—Among 8 cases, 13 assorated lesions were as follows: hydrothorax, 4; absence of the appendix, 2; and accessory lobe of the left lung, home acci-

dent, calculi of the kidneys, calculi of the prostate, decubital ulcer, lipidosis of the hematopoietic system, and minimal silicosis of the lungs, 1 each. The hydrothorax was bilateral in three cases and left-sided in one, the amount of fluid ranging from 100 to 500 cc. in either pleural cavity. The intertrochanteric fracture of the right femur sustained at home was 51 days after open reduction.

Brain Examination.—The brain was not examined in 15 cases and was examined and found to be negative in 5 cases.

G. Diabetes Mellitus

Sex and Age.—The six patients dying of diabetes mellitus were three men and three women, 80 to 89 years of age.

Cardiovascular Lesions.—Arteriosclerosis was significant in the coronary arteries in three cases, in the arteries of the lower extremities in two, and in the cerebral arteries in one.

The three cases of coronary arteriosclerosis showed, respectively, stenosis of the left coronary artery with mural thrombosis of the left ventricle of the heart, stenosis of the right coronary artery with old and recent infarcts of the left ventricle, and organized thrombosis of both coronary arteries with an old infarct of the left ventricle. Hypertrophy of the heart, weight 420 and 500 gm., was observed in two of these cases, edema of the lungs in two, and dilatation of the heart, bilateral hydrothorax, 1,500 cc. of fluid each, or acute passive hyperemia of the liver, in one each.

Of the two patients with arteriosclerosis of the arteries of the lower extremities, one had stenosis of the right popliteal artery and gangrene of the right foot several years after operation, and the other had thrombosis of the right tibial arteries and gangrene of the right foot five months after operation. Both were treated by midthigh amputation of the affected extremity.

In the one case of cerebral arteriosclerosis, thrombosis of the right middle cerebral artery was associated with a recent infarct of the right parietal lobe of the brain.

Other cardiovascular lesions included amyloidosis of the heart; a thrombosed, saccular arteriosclerotic aneurysm of the descending thoracic segment of the aorta; edema of the lungs; hypertrophy of the heart, weight 475 gm., with fibrosis of the myocardium of the left ventricle, dilatation of the heart, and edema of the lungs; and a recent infarct of the spleen, one case each.

Related Lesions.—Hyalinization of the islets of the pancreas was observed in three cases, atrophy of the pancreas in two, hyaline arteriolosclerosis of the kidneys in two, and glomerulosclerosis of the kidneys in two (Bell, 1953 [6]).

Infection.—Chronic cystitis was found in three cases, acute ulcerative esophagitis in two, and aspirative bronchopneumonia in two.

Alimentary Tract Lesions.—Multiple calculi of the gallbladder were noted in two cases, chronic cholecystitis with multiple calculi in two, multiple diverticula of the large intestine in two, and early portal cirrhosis of the liver in one. Calculi of the common bile duct complicated one case of chronic cholecystitis.

Benign Tumors.—In two cases, a carcinoid tumor of the ileum and a 7 cm. cyst of the lower lobe of the right lung were observed.

Nonlethal Cancer.—One patient had an occult carcinoma of the prostate.

Nodular Hyperplasia of Prostate.—One patient showed this lesion and hypertrophy of the urinary bladder.

Miscellaneous Lesions.—The following assorted lesions were noted: accidental injuries, in two; and, in one case each, operative absence of uterus, tubes, and ovaries, calculi of the urinary bladder, a decubital ulcer, focal necrosis of the adrenal cortex, minimal silicosis of lungs and bronchial lymph nodes, and a postoperative state 62 days after lumbar sympathectomy. One accident, sustained at home, resulted in an intertrochanteric fracture of the left femur, which was treated by open reduction 37 days before death. The other accident, sustained in the hospital, resulted in a fracture of the

neck of the right femur, which was not treated.

Brain Examination.—The brain was not examined in two cases, was examined and found negative in three, and showed a recent infarct in one, as given above.

H. Diseases of Nervous System

CASE 1.—Man, 83. Poliomyelitis, healed, spinal cord, active 69 years before; hypertrophy, urinary bladder; chronic cystitis; cystostomy; chronic suppurative ureteritis and pyelonephritis; atrophy, muscles, right leg and foot; bronchopneumonia, severe; brain not examined.

CASE 2.—Man, 82. Degeneration, basal ganglia and substantia nigra, brain; paralysis agitans, clinical; bronchopneumonia; hydrothorax (right, 500 cc. of fluid; left, 500 cc. of fluid); mural thrombosis, left atrium, heart; atrophy, liver, weight 920 gm.; calculi, gallbladder; diverticula, sigmoid segment, large intestine; septate urinary bladder.

I. Diseases of Respiratory Tract

CASE 1.—Man, 82. Emphysema, lungs; hypertrophy, right-sided, heart (thickness right ventricle, 8 mm.; weight 350 gm.); dilatation, right chambers, heart; chronic passive hyperemia, liver; bronchopneumonia, upper lobe, right lung; embolism, pulmonary artery branches, lungs; nodular hyperplasia, prostate; occult carcinoma, prostate; hypertrophy, urinary bladder; diverticula, sigmoid segment, large intestine; brain not examined.

CASE 2.—Woman, 81. Emphysema, lungs; perforation, bulla, upper lobe, left lung; bilateral pneumothorax, clinical; collapse, lower lobes, lungs; thoracotomy wounds (2), small, right second and left first intercostal spaces; emphysema, mediastinum and thoracic soft tissues; recent tracheostomy; chronic suppurative cholecystitis; calculi, gallbladder; cholecystectomy six days after operation; arteriosclerotic aneurysm, abdominal segment, aorta; 2 cm. chronic ulcer, fundus, stomach; 45 mm. leiomyoma, uterus; brain examined and negative.

J. Summary of Associated Diseases and Lesions

Included in this tabulation will be contributory causes of death, incidental cancers, benign tumors, alimentary tract lesions, and miscellaneous lesions, as observed in the sections entitled Essential Hypertension, Arteriosclerosis, Amyloidosis of Heart, Embolism of Lungs, Calcification of Heart Valves, Aneurysm of Cerebral Arteries, Miscellaneous Cardiovascular Diseases, Cancer, Infection, Accident, Nodular Hyperplasia of Prostate, Alimentary Tract Diseases, Diabetes Mellitus, Nervous System Diseases, and Respiratory Tract Diseases.

Essential Hypertension.—In addition to the 66 cases in which essential hypertension was responsible for death, this disease [7] was noted in 15 other cases, as follows: accidents, 7; alimentary tract diseases, 4; cancer, 3, and infection, 1.

Arteriosclerosis.—In addition to the 25 cases of *coronary arteriosclerosis* in which this lesion was the principal cause of death [28] and to the 22 cases of essential hypertension in which coronary arteriosclerosis was a paramount feature, 22 cases—6 of cancer, 4 of accident, 4 of infection, 3 of arteriosclerosis of cerebral arteries, 3 of diabetes mellitus, and 2 of nodular hyperplasia of prostate—showed coronary arteriosclerosis and related lesions, such as stenosis or thrombosis, myocardial infarction, mural thrombosis of atria or ventricles, edema of lungs, hydrothorax, and passive hyperemia of liver.

In addition to the nine cases of *cerebral arteriosclerosis* in which this lesion [12] was the principal cause of death, 15 cases—essential hypertension, 9; cancer, 2; infection, 2; alimentary tract diseases, 1, and arteriosclerosis of other arteries, 1—showed cerebral arteriosclerosis and related lesions, such as stenosis or thrombosis and cerebral infarction.

In addition to the one case of *aortic arteriosclerosis* in which this lesion was the principal cause of death,[32] 20 cases—6 of essential hypertension, 3 of arteriosclerosis of other arteries, 3 of cancer, 2 of accident, 2 of nodular hyperplasia of prostate, 2 of infection, 1 of alimentary tract diseases, and 1 of miscellaneous cardiovascular diseases—showed arteriosclerotic mural thrombosis of the aorta.

In addition to the four cases of *arteriosclerosis of arteries of the lower extremities*, 10 cases—essential hypertension, 4; diabetes mellitus, 2, and alimentary tract diseases,

arteriosclerosis of cerebral arteries, cancer, and nodular hyperplasia of prostate, 1 each —showed arteriosclerosis of the arteries of the lower extremities[5] and related lesions, such as gangrene of the legs and feet, often treated at variable intervals before death by midthigh amputation of the affected extremity.

In addition to the one case of *arteriosclerosis of the superior mesenteric artery*, one case of arteriosclerosis of other arteries showed this lesion and gangrene of the ileum.

Arteriosclerotic Aneurysm of Aorta.—In addition to the one case of perforated arteriosclerotic aneurysm of the aorta in which this lesion[10] caused death, 6 cases—2 of alimentary tract diseases, 1 of arteriosclerosis of other arteries, 1 of diabetes mellitus, 1 of essential hypertension, and 1 of respiratory tract diseases—showed arteriosclerotic aneurysm of the aorta.

Infarcts.—In addition to the one case of infarct of the brain noted under miscellaneous cardiovascular diseases, in which this lesion caused death, 34 other infarcts, not related to demonstrated arterial stenosis or thrombosis, included 13 of the spleen, 9 of the kidneys, 7 of the brain, 2 of the heart, and 1 each of the adrenals, lungs, and intestine. Most of these infarcts were recent; 16 were associated with essential hypertension; 9, with arteriosclerosis; 5, with accident; 2, with miscellaneous cardiovascular diseases; 1, with alimentary tract diseases, and 1, with diabetes mellitus.

Arteriolosclerosis of Kidneys.—When the 66 cases of essential hypertension and the 20 unsatisfactory cases are subtracted from the total 356 cases, 80 years of age and older in this study, 270 cases remain, of whom 10—4 of alimentary tract diseases, 3 of accident, 2 of arteriosclerosis, and 1 of nodular hyperplasia of prostate—or 3.7%, showed hypertrophic medial arteriolosclerosis of the kidneys. This compared with an incidence of 80.3%, or 53 of the 66 cases of essential hypertension for this lesion.[20]

Amyloidosis of Heart.—In addition to the 7 cases in which this lesion was the principal cause of death, 12 cases—3 of infection, 2 of alimentary tract disease, 2 of arteriosclerosis, 2 of cancer, and 1 each of miscellaneous cardiovascular disease, diabetes mellitus, and nodular hyperplasia of prostate —showed slight to severe amyloidosis of the heart. Of these, 4 were in addition to the 17 already described.[21] They were not recognized until study of sections of heart of all 336 satisfactory cases in this study were examined. Amyloidosis of the heart was not listed as part of the anatomic diagnosis of these four cases in the original protocols. This anatomic diagnosis served as the guide for the selection of the original 17 cases of this lesion reported.[21] Of the four new cases, amyloidosis of the heart caused death in one; in the other three, recent infarcts of the brain, chronic suppurative bronchopneumonia, and nodular hyperplasia of the prostate were the chief causes of death.

Embolism of Lungs.—In addition to the 6 cases in which this lesion was the only discerned principal cause of death, 71 cases —15 of accident, 14 of cancer, 12 of essential hypertension, 9 of arteriosclerosis, 9 of nodular hyperplasia of the prostate, 7 of infection, 2 of calcification of heart valves, 2 of miscellaneous cardiovascular diseases, and 1 of respiratory tract diseases—showed embolism of the lungs,[14,33] contributing to death. The emboli were large in 27 cases, medium in 23, and small in 21. The small emboli involved small branches of pulmonary arteries to one or two lobes of the lungs; the medium, the pulmonary artery branches to one or two lobes of the lungs, and the large, the right pulmonary artery, or the left pulmonary artery, or both. Recent pulmonary infarcts were associated in 26 of the 71 cases. Possible sources of the emboli noted in 18 of the 71 cases included thrombosis of the right atrium, in 10; of the iliac veins, in 4; of the adrenal veins, in 1; of the femoral veins, in 1; of the prostatic veins, in 1, and of the inferior vena cava, in 1. In the remaining 53 cases, the deep veins of the legs were the probable source for the emboli.

Benign Tumors.—The following 98 benign tumors were observed: polyp, 27; leiomyoma, 26; cyst, 19; adenoma, 7; cystadenoma, 6; carcinoid tumor, 4; hemangioma, 3; papilloma, 3; hamartoma, 1; pancreatic heterotopia, 1, and lipoma, 1. The location of the 98 benign tumors was as follows: kidney, 14; myometrium, 13; stomach, 12; endometrium, 10; small intestine, 10; large intestine, 9; adrenals, 4; ovary, 4; cervix, 3; pituitary, 3; bladder, 2; liver, 2; lungs, 2; pancreas, 2, and arachnoid, breast, esophagus, peritoneum, parathyroid, skin, thymus, and thyroid, 1 each.

The types of cases with which these benign tumors were associated were as follows: cancer, 19; accident, 16; essential hypertension, 16; infection, 10; arteriosclerosis, 8; alimentary tract diseases, 7; miscellaneous cardiovascular diseases, 6; nodular hyperplasia of prostate, 5; embolism of lungs, 4; aneurysm of cerebral arteries, 2; diabetes mellitus, 2; amyloidosis of heart, 1; calcification of heart valves, 1, and respiratory tract diseases, 1.

Nonlethal Cancers.—The 41 incidental cancers, classified as 38 carcinomas, 2 sarcomas, and 1 carcinoid tumor metastatic to liver, were distributed as follows: prostate, 21; skin, 4; large intestine, 3, and bladder, breast, duodenum, endometrium, esophagus, hematopoietic system, ileum, kidney, liver, pancreas, penis, peritoneum, and stomach, 1 each.

The types of diseases with which these 41 nonlethal cancers were associated were as follows: essential hypertension, 14; infection, 8; cancer, 6; accident, 5; arteriosclerosis, 3; nodular hyperplasia of prostate, 2; diabetes mellitus, 1; embolism of lungs, 1, and respiratory tract diseases, 1.

Bronchopneumonia.—In addition to the 31 cases in which moderate to severe pyogenic bronchopneumonia was the principal cause of death, this lesion [36] contributed to death in 70 cases in which the chief cause of death was as follows: cancer, 16; accident, 12; nodular hyperplasia of prostate, 12; arteriosclerosis, 11; essential hypertension, 6; alimentary tract diseases, 4; miscellaneous cardiovascular diseases, 2; embolism of lungs, 2; nervous system diseases, 2; amyloidosis of heart, 1; infection, 1, and respiratory tract diseases, 1.

Cystitis.—In 94 cases, cystitis (Karsner, 1949 [15]), usually chronic, was associated with the following: nodular hyperplasia of prostate, 24 cases; infection, 15; cancer, 14; accident, 11; essential hypertension, 9; arteriosclerosis, 8; alimentary tract diseases, 4; diabetes mellitus, 3; embolism of lungs, 2; miscellaneous cardiovascular diseases, 2; calcification of heart valves, 1, and nervous system diseases, 1.

Pyelonephritis.—In 23 cases, pyelonephritis (Bell, 1950 [4]), often chronic or acute suppurative, was noted in association with the following causes of death: nodular hyperplasia of prostate, 11; cancer, 8, and accident, alimentary tract diseases, arteriosclerosis, and nervous system diseases, 1 each.

Esophagitis.—In 28 cases, esophagitis (Bartels, 1935 [3]), most frequently acute ulcerative, occurred as a contributing cause of death with the following: accident, 6; cancer, 4; essential hypertension, 4; nodular hyperplasia of prostate, 4; alimentary tract diseases, 3; infection, 3; arteriosclerosis, 2, and diabetes mellitus, 2.

Accident.—In addition to the 43 cases in which accidents were the chief cause of death, accidents were of variable significance in contributing to death from other causes in 28 cases, as follows: cancer, 6; infection, 5; essential hypertension, 5; arteriosclerosis, 4; accident, 2; diabetes mellitus, 2; nodular hyperplasia of prostate, 2; alimentary tract diseases, 1, and miscellaneous cardiovascular diseases, 1.

Nodular Hyperplasia of Prostate.—In addition to 29 cases in which this lesion was the principal cause of death, 63 other cases showed significant nodular hyperplasia of the prostate,[19] associated with the following: essential hypertension, 17; infection, 13; accident, 8; arteriosclerosis, 8; alimentary tract diseases, 6; cancer, 6; miscellaneous

cardiovascular diseases, 2; diabetes mellitus, 1; embolism of lungs, 1, and respiratory tract diseases, 1. Of these 63 cases, 41 showed hypertrophy of the urinary bladder; 8, diverticulum of the urinary bladder; 3, infarcts of the prostate, and 16, operations, usually some type of prostatic resection, at variable intervals before death.

Diabetes Mellitus.—In addition to the six patients in whom diabetes was the cause of death, two patients showed this disease, one with essential hypertension and one with nodular hyperplasia of the prostate.

Atrophy of Liver.—In 58 cases, the liver was atrophic, weight 600 to 1,015 gm., with the following causes of death: accident, 11; essential hypertension, 10; infection, 10; arteriosclerosis, 7; cancer, 5; nodular hyperplasia of prostate, 5; alimentary tract diseases, 4; miscellaneous cardiovascular diseases, 2; amyloidosis of heart, 1; aneurysm of cerebral arteries, 1; calcification of heart valves, 1, and nervous system diseases, 1.

Fatty Metamorphosis of Liver.—In 14 cases, this lesion was associated as follows: accident, 4; infection, 4; essential hypertension, 2; aneurysm of cerebral arteries, 1; alimentary tract diseases, 1; arteriosclerosis, 1, and miscellaneous cardiovascular diseases, 1.

Acute Central Necrosis of Liver.—This focal lobular or sublobular lesion (Dubin, 1947 [11]) was observed in 10 cases, in association with the following causes: essential hypertension, 4; cancer, 2; infection, 2; alimentary tract diseases, 1, and nodular hyperplasia of prostate, 1.

Cirrhosis of Liver.—In eight cases, cirrhosis (Popper and Schaffner, 1957 [25]) was portal in five and cardiac in three. The five cases of portal cirrhosis were observed in one case each of the following: accident, amyloidosis of heart, diabetes mellitus, essential hypertension, and nodular hyperplasia of prostate. The three cases of cardiac cirrhosis were observed in one case each of the following: arteriosclerosis, calcification of heart valves, and essential hypertension.

Calculi of Gallbladder.—Calculi (Phemister et al., 1939 [21]; Riegel et al., 1936 [20]) were observed in 54 cases, in association with the following: essential hypertension, 11; cancer, 10; infection, 7; accident, 6; arteriosclerosis, 6; nodular hyperplasia of prostate, 5; alimentary tract diseases, 4; diabetes mellitus, 2; aneurysm of cerebral arteries, 1; embolism of lungs, 1, and nervous system diseases, 1. The calculi, usually multiple, were of the pigment type in 16 cases and, from the description available, were of the mixed type in the remainder. No instance of carcinoma of the gallbladder coexisted with the calculi.

Cholecystitis.—This lesion [1] was found in 38 cases as follows: accident, 9; essential hypertension, 7; cancer, 6; infection, 3; nodular hyperplasia of prostate, 3; alimentary tract diseases, 2; amyloidosis of heart, 2; arteriosclerosis, 2; diabetes mellitus, 2; miscellaneous cardiovascular diseases, 1, and respiratory tract diseases, 1. The cholecystitis was chronic in 34, chronic suppurative in 3, and acute in 1. Calculi, of pigment type in 8 and mixed type in 23, were noted in 31 cases. No instance of carcinoma of the gallbladder was coexistent.

Diverticula of Intestine.—In 50 cases, such lesions were distributed as follows: accident, 9; cancer, 8; infection, 8; arteriosclerosis, 7; essential hypertension, 6; alimentary tract diseases, 5; diabetes mellitus, 2; nodular hyperplasia of prostate, 2; miscellaneous cardiovascular diseases, 1; nervous system diseases, 1, and respiratory tract diseases, 1.

Peptic Ulcer.—In 12 cases, 7 duodenal and 5 gastric ulcers (Boles and Dunbar, 1946 [8]) were distributed as follows: cancer, 3; essential hypertension, 2; nodular hyperplasia of prostate, 2, and accident, amyloidosis of heart, arteriosclerosis, infection, and respiratory tract diseases, 1 each.

Decubital Ulcer of Skin.—In 25 cases, this lesion was distributed as follows: accident, 10; arteriosclerosis, 5; essential hypertension, 3; infection, 2; nodular hyperplasia of prostate, 2; alimentary tract diseases, 1;

miscellaneous cardiovascular disease, 1, and diabetes mellitus, 1.

Operative Absence of Organs.—In 38 cases organs, usually the appendix or gallbladder, were operatively absent for varying periods before death. Details are available in each of the 15 sections constituting the body of this report.

Comment

In an analysis of the population of the United States, Smith (1955 [29]) noted that persons 65 years of age and older constituted 4.1% of the population in 1900 and 8.1% in 1950, a rise of 297%, as compared with an increase of only 98% for the population as a whole. In 1950 in Colorado, persons 65 years of age and older accounted for 8.7% of the population. This compares with the 9.5% of persons 80 years of age and older for the five-year period, 1945-1950, of this study. He predicted that persons 65 years of age and older would constitute 9.8% of the population of the United States by 1970. He attributed 56% of the gain in the number of persons 65 to 74 years of age between 1940 and 1950 to the post-Civil-War rise in birth rate; 21.5%, to gradual aging of European immigrants arriving in the United States before World War I, and 19% to increased life expectancy. His study leaves no doubt that a gradual increase of the elderly population of the United States is inevitable, barring national catastrophe, although the sharp increase in birth rate during and after World War II may slow the proportionate rise of the number of oldsters in the decades ahead.

The most integrated, if not the most comprehensive, autopsy study of persons 80 years of age and older found in the literature, and in many respects comparable to mine, is that of Groddeck (1939 [13]), who described the findings in 283 autopsies (2.5% of 11,552 made at the Institute of Pathology of the University of Rostock between 1921 and 1938) on patients, 144 men and 139 women, over 80 years of age. These cases were divided as follows: cardiovascular disease, 105; accident, 44; infection, 39; cancer, 35; alimentary tract disease, 26; nodular hyperplasia of prostate, 23; urinary tract disease, 6, and diabetes mellitus, 5. The 105 cases of cardiovascular disease included arteriosclerosis of the coronary, cerebral, pulmonary, lower extremity, or renal arteries; cerebral hemorrhage, and syphilitic aortitis. The accident cases were divided as follows: fracture, 35 (femur, 29); suicide, 4; burns, 2; laceration of viscera, 2, and mushroom poisoning, 1. The 39 cases of infection were distributed as follows: pneumonia, bronchiectasis, or lung abscess, 23; tuberculosis, 8; and septicemia, usually related to cellulitis of lower extremities, 8. The 35 cases of cancer were classified as 32 carcinomas and 3 sarcomas, affecting the stomach in 7 cases, the large intestine in 6, the lip in 4, the lung in 3, the pancreas in 3, the ovary in 2, the prostate in 2, and the arm, urinary bladder, breast, duodenum, gallbladder, skin, small intestine, and an unstated organ, 1 each. The 26 cases of alimentary tract diseases were divided as follows: hernia, 10; cirrhosis of liver, 4; ileus, 4; peptic ulcer, 4; enteritis, 3, and starvation, 1. Of 48 cases in which embolism of the lungs was of auxiliary lethality, the sources for the emboli in 41 cases were as follows: femoral veins, 19; prostatic or uterine veins, 9; femoral and other veins, 5; iliac veins, 3; heart, 3, and pelvic veins, 2. The source was not determined in 7. Of the 14 nonlethal cancers, 5 were primary in the prostate, 3 in the large intestine, 2 in the breasts, 2 in the kidneys, and 1 each in the duodenum and stomach. With the exception of the smaller number of deaths from cancer and of nonlethal cancers in Groddeck's series,[13] the incidence of all other leading causes of death was comparable to that found in my series.

Among 50 autopsied psychotic patients, 30 women and 20 men, 80 to 94 years of age, Strassmann and Krush (1947 [31]) observed the following proximate causes of death: bronchopneumonia, 33; embolism of lungs related to femoral vein thrombosis,

7; carcinoma, 4 (stomach, 2; cervix, 1; prostate, 1); arteriosclerotic coronary thrombosis, 4, and tuberculosis, 2. Also observed were infarcts of the brain, in 34 cases (lenticulostriate area, 21; lobes of hemispheres, 8, and cerebellum 5); emaciation, in 30 (faulty food intake, 24; cancer or tuberculosis, 6); decubital ulcer, in 25; fibrosis of myocardium, in 20; chronic cholecystitis and cholelithiasis, in 14; acute ulcerative esophagitis, gastritis, or duodenitis, in 8; myometrial leiomyoma, in 8; small subdural hematoma, in 6; mural thrombosis of aortic or mitral valves of heart, in 5; atrophy of brain weight 840 to 980 gm., in 3; thrombosed arteriosclerotic aneurysm of the aorta, in 2, and endometrial polyp, in 2.

Negri and Palazzuoli (1951 [22]) studied 1,410 autopsies of patients, 662 men and 748 women, over 80 years old. They observed the following distribution of lesions: pneumonia, in 887 cases; lesions of the aorta, in 407, fibrosis of the myocardium, in 301, hypertrophy of the heart, in 253; cancer, in 172; infarcts of the brain, in 115; biliary calculi, in 100; lesions of the cardiac valves, in 88; nodular hyperplasia of the prostate, in 88; tuberculosis of the lungs, in 81; cholecystitis, in 63; cerebral hemorrhage, in 47; endocarditis, in 45; pyelonephritis, in 35; peptic ulcer, in 18, and recent infarct of the heart, in 8. They noted only two cases of hematopoietic disease, one of myeloid leukemia and the other of pernicious anemia. Of the 887 cases of pneumonia, 715 were bronchial and 172 were lobar. The 407 aortic lesions included 368 of severe arteriosclerosis, 21 of syphilitic aortitis, 17 of aneurysm, and 1 of suppurative aortitis. The 172 cancers included 161 carcinomas and 11 sarcomas. The carcinomas were distributed as follows: stomach, 75; large intestine, 16; pancreas, 10; breast, 8; biliary ducts, 7; uterus, 5; urinary bladder, 5; liver, 5; thyroid, 5; skin, 4; prostate, 4; kidney, 3; ovary, 2; esophagus, 2; small intestine, 2; renal pelvis, 2, and larynx, lip, oral cavity, adrenal, vulva, and penis, 1 each. The 88 lesions of the cardiac valves were classified as follows: postendocarditis, 61; arteriosclerosis, 26, and syphilis, 1. The 63 cases of cholecystitis were chronic in 47 and acute or subacute in 16. The 45 cases of endocarditis were acute in 30 and subacute in 15. The 18 cases of peptic ulcer were found in the stomach in 15 and in the duodenum in 3. In their statistical compilation, these authors did not distinguish principal and auxiliary causes of death, unless all 172 cancers listed could be assumed to be lethal. With this possibility allowed, the incidence of cancer in their series was 12.2%, as compared with 12.4 in Groddeck's series and 16.3 in mine.

Keck (1955 [17]) described the autopsy findings in 60 persons, 25 men and 35 women, over 90 years old. The causes of death were as follows: bronchopneumonia, in 24; cardiovascular disease, in 20; infection, in 6; cancer, in 5, and encephalomalacia, in 5. He emphasized the low incidence of cancer in this group as compared with that for bronchopneumonia. Among the patients dying of bronchopneumonia were three men with severe emphysema of the lungs. The 20 cases of cardiovascular disease were divided as follows: pulmonary embolism, 8; large fibrotic cardiac aneurysm, 5; left-sided cardiac failure, 4; right-sided cardiac failure, 2, and verrucous endocarditis of the mitral valve, 1. The absence of recent cardiac infarcts in this group was noteworthy. The six cases of infection included three of lobar pneumonia, one of empyema of a pleural cavity, and one of fibrinopurulent peritonitis. The five cases of cancer were accounted for by three carcinomas of the large intestine and two carcinomas of the prostate. Five incidental carcinomas were primary in the lungs in two, in the prostate in two, and in the stomach in one. Among the 25 men, 17 showed nodular hyperplasia of the prostate, of whom 12 also had hypertrophy of the urinary bladder. During the period of the study, 1949-1954, at the Pathologic Institute of the General Hospital of Hamburg-Barmbek, Keck [17] noted a steady increase of

persons over 90 years of age in Hamburg, with a distribution of about one-third men and two-thirds women. His study was the only survey of causes of death in persons over 90 years of age found in the literature up to the end of 1957.

In Column 1 of Table 3 are listed the major diseases found in 304 of the series of 336 satisfactory cases. In Column 2 are noted those cases in which these diseases were the principal cause of death. In Column 3, these diseases are analyzed with respect to these 304 cases in which they were frequently a contributory cause of death, or less often incidental. In Column 4, Columns 2 and 3 are added for each disease. In Column 5 is the percentage calculated by dividing the number of cases in Column 2 by those in Column 4. This percentage represents the frequency with which a patient with a given disease died with this disease as the principal cause of death. For instance, among the 80 cases of essential hypertension, this disease was the principal cause of death in 66 cases, or 82.5% of the total of 80 cases with the features of this disease. ***Put simply, the percentage figures in Column 5 represent the chances of a person with a given disease listed in Column 1 of dying of this disease.*** The remaining 32 cases of the 336 satisfactory cases not listed in Column 2 included the 3 with calcification of heart valves, the 2 with congenital aneurysm of cerebral arteries, the 5 with miscellaneous cardiovascular lesions, the 13 with infections other than bronchopneumonia, the 2 with starvation, the 1 with adhesion of peritoneum, the 1 with hernia, the 1 with stricture of the esophagus, the 2 with diseases of the nervous system, and the 2 with diseases of the respiratory tract.

By way of contrast, cystitis, in 94 cases; pyelonephritis, in 23 cases; esophagitis, in 28 cases; acute central necrosis of the liver, in 10 cases; cirrhosis of the liver, in 8 cases; calculi of the gallbladder, in 54 cases, and decubital ulcer in the skin, in 25 cases, were always contributory causes of death or incidental in the total series of 336 satisfactory cases.

Summary

1. In the 15-year period between 1940 and 1955, autopsies on 356 persons, 253 men and 103 women, 80 years of age and older comprised 10.5% of all autopsies, exclusive of the newborn and stillborn, at the Colorado General Hospital. The percentage of autopsies in this group almost doubled in the third semidecade as compared with the first semidecade of this period, or from 7.5% to 14.1%.

2. The relative frequencies of death from various diseases in the 336 satisfactory cases were as follows: cardiovascular disease, 64; cancer, 29; infection, 22; accident, 21.5; nodular hyperplasia of prostate, 14.5; alimentary tract disease, 10; diabetes mellitus, 3; nervous system disease, 1, and respiratory tract disease, 1.

3. The 132 cases of cardiovascular disease were classified as follows: essential hypertension, 66; arteriosclerosis, 43 (coronary, 25; cerebral, 9; arteries of lower extremities, 4; pulmonary arteries, 3; superior mesenteric artery, 1, and aorta, 1); amyloidosis of heart, 7; embolism of lungs, 6; calcification of heart valves, 3; congenital aneurysm of cerebral arteries, 2, and miscellaneous, 5.

4. The 59 cancers in 58 cases of cancer were distributed as follows: prostate, 16; stomach, 7; large intestine, 6; skin, 5; hematopoietic system, 4; lungs, 4; pancreas, 4; breasts, 3; pharynx, 3; and cystic duct, urinary bladder, jejunum, larynx, liver, palate, and, thyroid gland, 1 each.

5. The 44 cases of infection were as follows: bronchopneumonia, 31; tuberculosis of lungs, 5; chronic abscess of lungs, 2, and acute cellulitis of an upper extremity, acute otitis media, acute suppurative meningitis, chronic abscess of a molar tooth socket, infectious hepatitis, and tuberculosis of the pericardium, 1 each.

6. The 43 cases of accident were as follows: fractures, 36 (femur, in 31); burns, 3, and suicide by gunshot, subdural hematoma, operative trauma to a ureter, and asphyxia, 1 each.

7. The 29 cases of nodular hyperplasia of the prostate exhibited obstruction and infection of the urinary tract, as well as inflammatory lesions of other organs, notably of the lungs.

8. The 20 cases with alimentary tract diseases were distributed as follows: peptic ulcer, 9; cholecystitis, 4; appendicitis, 2; starvation, 2; adhesion of peritoneum, 1; hernia, 1, and stricture of esophagus, 1.

9. The six patients with diabetes mellitus died of the effects of arteriosclerosis of coronary, lower extremity, or cerebral arteries.

10. The primary lesions in the two cases of nervous system diseases were healed poliomyelitis of the spinal cord, complicated by cord bladder and urinary tract infection, and degeneration of the basal ganglia and substantia nigra of the brain, complicated by bronchopneumonia.

11. The two cases of respiratory tract diseases included one patient with emphysema of the lungs with right-sided hypertrophy and dilatation of the heart, and congestive heart failure, and another patient with emphysema of the lungs with perforation of a bulla of one lung and bilateral pneumothorax.

12. The following contributory causes of death were observed: essential hypertension, in 15 cases; arteriosclerosis, in 48 (coronary, in 22; cerebral, in 15; arteries of lower extremities, in 10, and superior mesenteric artery, in 1); infarcts of various organs, in 34; embolism of lungs, in 71; brochopneumonia, in 70; cystitis, in 94; pyelonephritis, in 23; esophagitis, in 28; accident, in 28; nodular hyperplasia of prostate, in 29; fatty metamorphosis of liver, in 14; acute central necrosis of liver, in 10; cirrhosis of liver, in 8; peptic ulcer, in 12, and decubital ulcer of skin, in 25.

13. Lesions more frequently of correlative importance only were as follows: arteriosclerotic mural thrombosis of the aorta, in 20 cases; arteriosclerotic aneurysm of the aorta, in 6 cases; arteriolosclerosis of the kidneys, in 10 cases; amyloidosis of the heart, in 12; atrophy of the liver, in 58; calculi of the gallbladder, in 54; cholecystitis, in 38, and diverticula of the intestine, in 50.

14. Neoplasms of interest were 98 benign tumors and 41 nonlethal cancers.

15. In 304 of the 336 satisfactory cases, the percentage chance of a given disease being the principal cause of death was as follows: embolism of lungs, 8.6; cholecystitis, 10.5; arteriosclerotic aneurysm of aorta, 16.7; arteriosclerosis of arteries of lower extremities, 28.6; bronchopneumonia, 34.1; nodular hyperplasia of prostate, 34.9; arteriosclerosis of cerebral arteries, 37.5; amyloidosis of heart, 38.8; peptic ulcer, 45.0; arteriosclerosis of superior mesenteric artery, 50.0; arteriosclerosis of coronary arteries, 53.2; accident, 64.2; cancer, 65.9; diabetes mellitus, 75.0; essential hypertension, 82.5; appendicitis, 100.0, and arteriosclerosis of pulmonary arteries, 100.0.

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Experimental Arterial Lesions Produced by Reticuloendothelial Blocking Agents

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Studies of the effects of colloidal suspensions of macromolecular substances on the reticuloendothelial system, cholesterol metabolism, and the intima of some arteries have stimulated much conjecture, as well as conflicting opinion regarding the interrelationship of these three entities in experimentally produced arteriosclerosis and atherosclerosis.

Studies of the effects of reticuloendothelial system-blocking agents, such as carbon, thorium dioxide, iron, and silver, on plasma cholesterol levels have produced variable, and hence inconclusive, results. These studies have all been on the relatively short-term or transient effects of colloidal blocking agents on animals maintained on standard diets, high-cholesterol, or high-lipid diets or on animals which have received intravenous lipids.[1-12] In spite of the variable responses elicited, each of the investigators has recognized a relationship between lipid metabolism and reticuloendothelial cell function.

Phagocytosis of injected colloidal suspensions by endothelial cells or by macrophages of the intima of arteries has been observed.[13-21] The phagocytosis of the injected colloids by these cells has, in most instances, required massive or repeated injections of the foreign materials [14] or is dependent upon a slowing of the circulation.[19] Although it is recognized that the endothelial-cell response is secondary to that of the reticuloendothelial cell, no functional relationship or dependence between the two has been established.

The actual production of vascular lesions by the intravenous administration of colloidal suspensions has been reported by Lautsch [4] and by Hueper.[21] In both investigations the resultant vascular lesions were observed only in the aorta following relatively short-term experiments.

Materials and Methods

This series of experiments involved the injection of carbon (Higgins India ink) into the marginal ear veins in 75 young male rabbits. The dosage of each injection was 2 cc. of India ink for each 5 lb. of animal body weight, which is the equivalent of approximately 5 mg. of carbon for each 100 gm. animal body weight. Two series of time sequence studies were undertaken. In one series the animals received a single injection of carbon, and in the other series multiple injections were given. The times of animal killing were at postinjection periods of 5 minutes through 16 weeks. Control animals were given intravenous injection of colloidal thorium dioxide (Testagar & Company, Inc., Detroit) in the amount of 2 cc. per 5 lb. body weight.

In one group of six animals, blood plasma cholesterol determinations were made during a 12-week period following a single injection of carbon and liver cholesterol determinations were made after their killing. Another group of animals received single carbon injections three weeks after they had been maintained on a diet which included 1% added cholesterol, and a final series received 1% added cholesterol to their diets 12 weeks after having been given a single injection of carbon.

After the animals were killed, the liver, spleen, lung, bone, thyroid, lymph nodes, and heart and great vessels were removed, and these tissues were prepared for microscopic study by the usual techniques.

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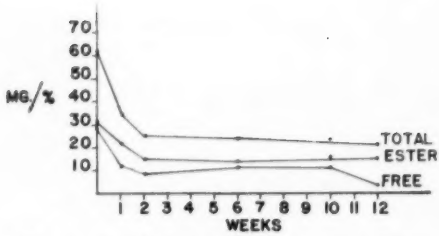

Fig. 1.—Blood plasma cholesterol levels following intravenous injection of 5 mg. of carbon (India ink) per 100 gm. animal body weight.

Observations

Following a single intravenous injection of carbon (5 mg. per 100 gm. body weight), the blood plasma cholesterol levels had dropped to about one-half their normal values at the end of two weeks and remained at this level for the remaining 10 weeks of the study (Fig. 1). The liver cholesterol determinations on these animals at the end of the 12-week period were within normal ranges. When 1% cholesterol was added to the diet, the blood plasma cholesterol levels rapidly rose to hypercholesteremic levels.

Pulmonary Arteries.—Within one week following a single injection of carbon, beginning changes were observed in the intima of some of the pulmonary arteries. The early changes involved a thickening of the intima and an increased number of endothelial cells and fibroblasts in the subendothelial tissues. The ground substance of the intima was increased in volume and appeared edematous, containing numerous small vacuoles (Fig. 2). The Gomori aldehyde-fuchsin elastic tissue stain revealed a splitting of the internal elastic membrane and beginning proliferation of elastic fibers in the intima (Fig. 3). Three weeks after the injection of carbon, the pulmonary arterial changes appeared identical with those changes produced in rabbits by the addition of cholesterol to their diet. The intima was considerably thickened, and there were cells which appeared to be typical foam cells. There was also an endothelial-cell hyperplasia and both collagenous- and elastic-fiber proliferation (Fig. 4). Beyond three weeks after the carbon injection, the structural organization of the plaques in the pulmonary arteries remained unchanged; however, they continued slowly to increase in thickness and extent. After 12 weeks, in some arteries, the intimal proliferation had considerably narrowed the lumina (Fig. 5). Opposite the intimal lesions there was also a slight increase in the number of elastic fibers of the media (Fig. 4). Although free carbon particles are occasionally seen in the intima of blood vessels, no particles were seen in or adjacent to the lesions.

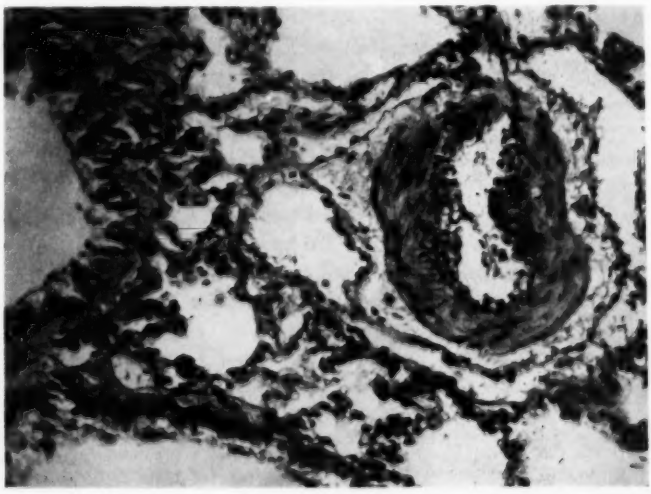

Fig. 2.—Pulmonary artery of rabbit less than one week after carbon injection. Early endothelial-cell proliferation is already evident. Hematoxylin and eosin; reduced to 92% of mag. ×250.

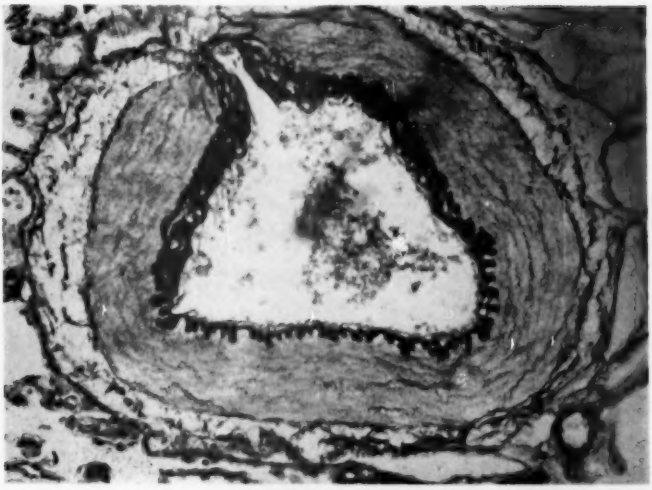

Fig. 3.—Pulmonary artery of rabbit one week after carbon injection. Beginning increase in elastic fibers of intima. Aldehyde-fuchsin stain; reduced to 92% of mag. × 75.

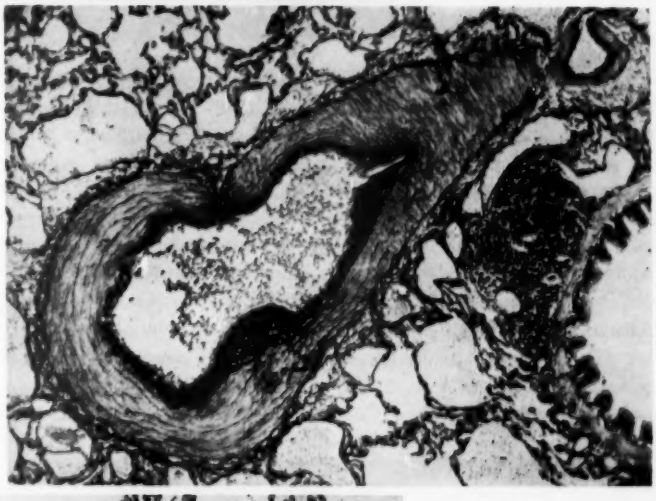

Fig. 4.—Pulmonary artery of rabbit three weeks after carbon injection. Early plaque formation in intima, as well as some increase in elastic fibers of the media opposite the intimal lesion. Aldehyde-fuchsin stain; reduced to 92% of mag. × 75.

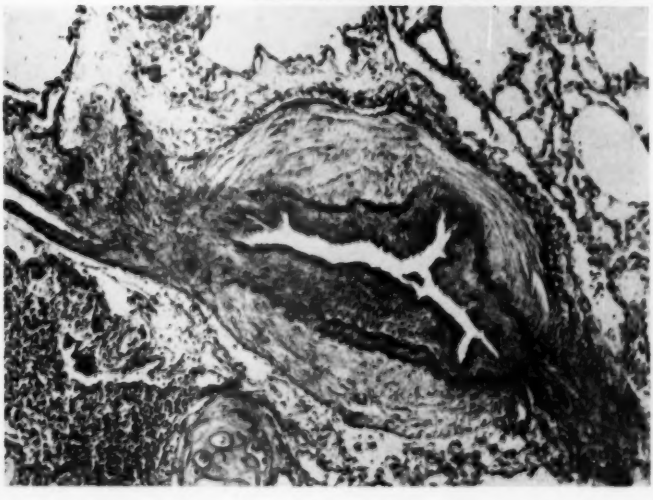

Fig. 5.—Pulmonary artery of rabbit 12 weeks after carbon injection. Advanced intimal proliferative changes. Aldehyde-fuchs'in stain; reduced to 92% of mag. × 125.

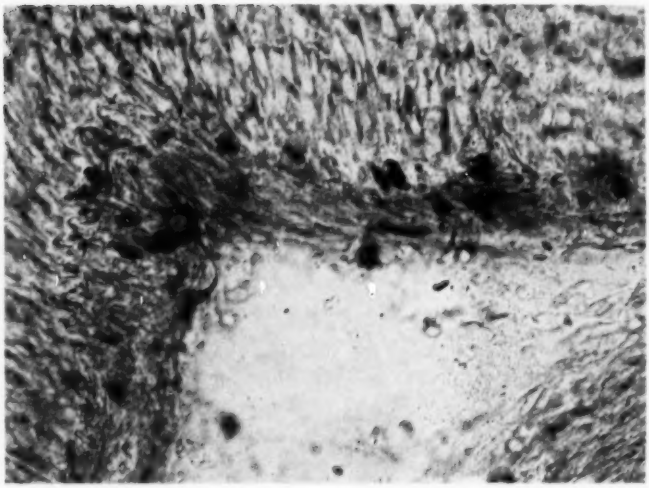

Fig. 6.—Pulmonary artery of rabbit 12 weeks after carbon injection, which was then made hypercholesteremic by 1% cholesterol added to its diet for five days. The stainable lipid has been, for the most part, phagocytosed by lipophages. Oil red O; reduced to 92% of mag. × 250.

In no instant was there with certainty positive identification of demonstrable lipid in the foam cells or the thickened intima of the pulmonary arterial lesions as long as the animals remained hypocholesteremic. Demonstrable lipid was found in the pulmonary arterial lesions of those animals which were given added cholesterol in their diet 12 weeks after having received carbon intravenously. The lipid was first detected on the fifth day after the beginning of cholesterol feeding or when the animal became hypercholesteremic. Although some free lipid was seen in the ground substance of the intima, it is most apparent in intimal macrophages (Fig. 6). Rabbits which received an injection of carbon after having been made hypercholesteremic by the addition of cholesterol to their diet revealed no changes in their pulmonary vascular intima which could not be accounted for by the hypercholesteremia alone. The single injection of carbon caused the same vascular changes in the same time sequences as did the multiple injections. All animals receiving single or multiple injections of car-

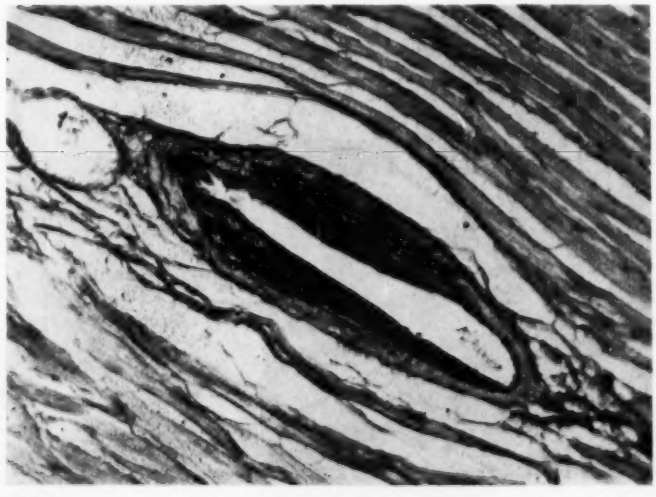

Fig. 7.—Coronary artery of rabbit four weeks after carbon injection. Early elastic-fiber proliferation in intima. Aldehyde-fuchsin stain; reduced to 92% of mag. × 250.

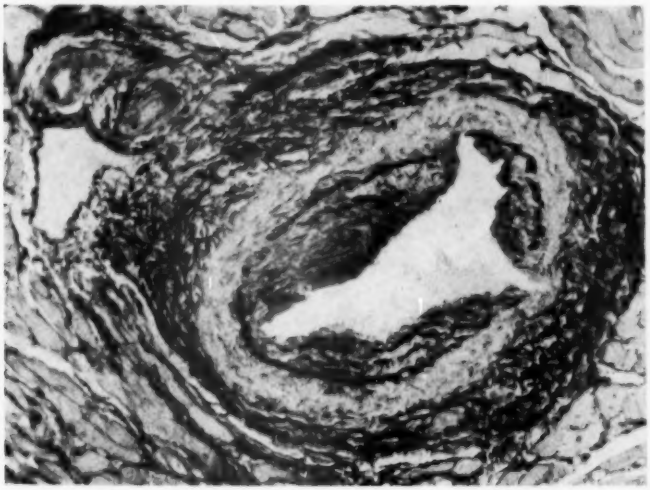

Fig. 8.—Coronary artery of rabbit six weeks after carbon injection. Elastic- and collagenous-fiber proliferation has caused a much thickened intima. Aldehyde-fuchsin stain; reduced to 92% of mag. × 250.

bon showed pulmonary vascular pathology of varying degrees. The illustrations are of the more advanced lesions for that particular time period. The pulmonary arteries of control rabbits which received an intravenous injection of Thorotrast contained lesions which appeared identical with those in rabbits which had received the carbon injection.

Coronary Arteries.—Four weeks after a single injection of carbon, changes in the intima of the coronary arteries were observed. These lesions differed from the pulmonary arterial lesions in that there was only a small increase in the number of subendothelial cells and the ground substance did not appear as edematous. There was, however, a more evident increase in the number of connective tissue elements, as well as an increased proliferation of collagenous and elastic fibers (Fig. 7). As the postinjection time sequence is prolonged, there is a marked progression in the severity of the vascular lesion; however, the cellular and fibrous organization remains essentially the same (Fig. 8). Figures 9 and 10 show the most advanced lesions in the hearts of ex-

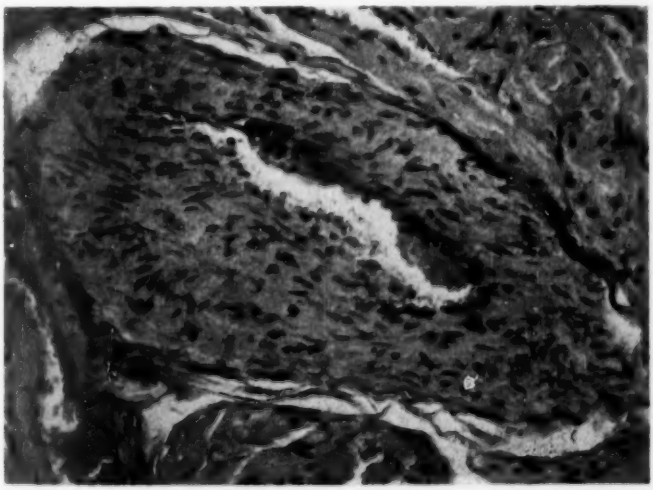

Fig. 9.—Coronary artery of rabbit 12 weeks after carbon injection. The proliferation of connective tissue elements has greatly thickened the intima. Hematoxylin and eosin; reduced to 92% of mag. × 250.

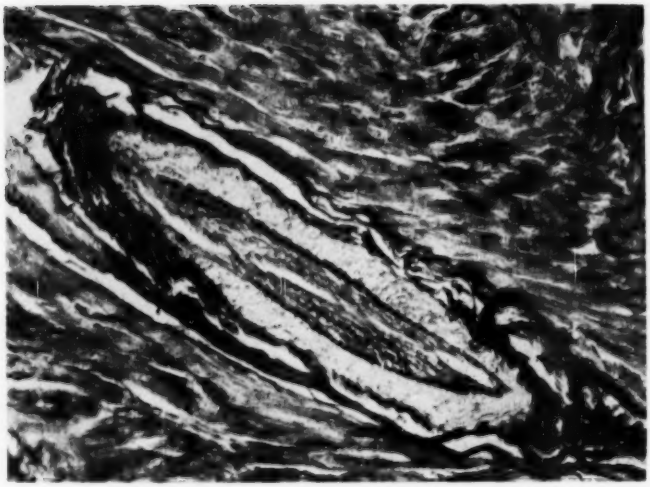

Fig. 10.—Coronary artery of rabbit 12 weeks after carbon injection. Proliferation of fibers in the intima leaves the lumen a mere slit. Aldehyde-fuchsin stain; reduced to 92% of mag. × 250.

perimental animals 12 weeks after having received a single injection of carbon. Owing to the extensive proliferation of connective tissue and elastic fibers, the lumina of these vessels have become only a slit. The media of the involved arteries remained relatively unchanged. As in the pulmonary arteries, no free carbon was located in or adjacent to the areas of pathology, and multiple injections of carbon did not alter the character of the lesions. Here, also, coronary vascular lesions were observed in all animals injected. Those control animals which received Thorotrast revealed lesions identical with those in the series which were given carbon.

Demonstrable lipid was observed in the altered intima, as well as in flattened subendothelial foam cells of the coronary arteries of only those animals which received oral cholesterol added to their diets 12 weeks following an intravenous carbon injection. The stainable lipid, as was the case in the pulmonary arteries, could not be detected until the fifth day of cholesterol feeding. In contrast to the appearance of

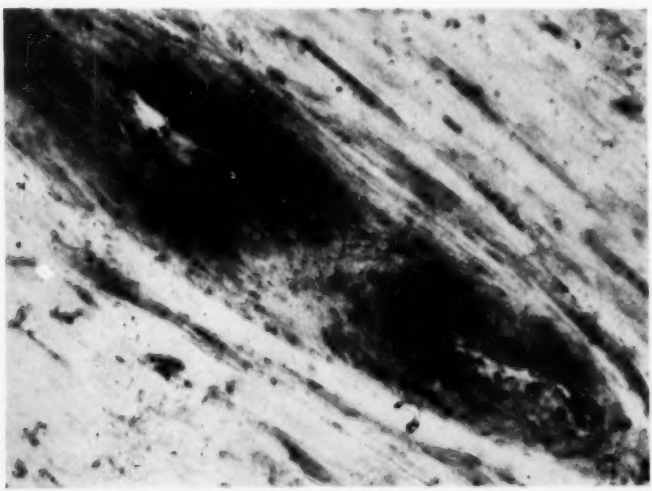

Fig. 11.—Coronary artery of rabbit 12 weeks after carbon injection, which was then made hypercholesteremic by the addition of 1% cholesterol to its diet for five days. The stainable lipid is for the most part deposited in the ground substance of the intima and to some extent in the media. Only a few cells containing lipid are seen. Oil red O; reduced to 92% of mag. × 500.

lipid in pulmonary arteries, the coronary arteries exhibited most of the stainable lipid in the ground substances. Macrophages containing this material are seen only occasionally in the prepared sections (Fig. 11).

Heart and Aorta.—In several animals small atheromatous-like lesions were observed in the endocardium at the bases of the aortic and mitral valves six weeks following the intravenous carbon injection. No structural changes were found in the intima of the aortas of the experimental animals which received a carbon injection and were maintained on the standard rabbit diet.

Comment

This series of experiments has demonstrated that intimal changes resembling atherosclerosis were produced in the pulmonary and coronary arteries after the intravenous injection of either carbon or Thorotrast. Also, these vascular changes were produced at a time when the animals were hypocholesteremic. Whether these vascular changes are called atherosclerotic or arteriosclerotic is purely a matter of definition. Perhaps they should be called "preatherosclerotic." During the period when the animals were hypocholesteremic, no lipid was demonstrable in the intimal lesions; if the blood plasma cholesterol levels were raised to hypercholesteremic levels, however, lipid was demonstrated in the lesions. Cholesterol was added to the diet of the experimental animal 12 weeks after the injection of carbon. Therefore, it must be assumed that the vascular lesions had already developed, since their first appearance was within three weeks after carbon injection. Also, since lipid was demonstrated in the vascular lesions of animals killed five days only after the beginning of the cholesterol feeding, it must be concluded that the lesions could not have been produced by the hypercholesteremia alone, such lesions requiring at least three weeks of hypercholesteremia for their development.[24]

Any explanation of either the vascular intimal pathology or the hypocholesteremia as a result of the intravenous injection of carbon or other macromolecular particles is presumably related in part to the effect of these materials on the reticuloendothelial system. This system of macrophages, as far as has been demonstrated, is the most responsive of all tissues to macromolecular substances which have been experimentally introduced into the blood stream.[23] Also, it is known, and has again been observed in the present investigation, that these substances are retained within the reticuloendothelial cells for a long period of time, if not for the remainder of the life of the animal.[23] That these cells are involved in the uptake and metabolism of cholesterol has also been demonstrated.[2,6,12] Hence, it may be inferred that the carbon particles phagocytosed by the reticuloendothelial cells in these experiments altered the normal metabolism of lipids by these cells, as evidenced by the low plasma cholesterol. Another consideration to be resolved is the fact that the reticuloendothelial cells of the liver, as the lining cells of the hepatic sinusoids, form the primary membranes for the passage of substances between liver parenchyma and the blood stream. Alteration of these sinusoidal cells may therefore interfere with normal liver function, and hence lipid metabolism.[2,6,12] These experiments also lend support to the opinion that the endothelial cell is not a completely differentiated cell, but forms the "second line of defense"[13] when the reticuloendothelial system is overburdened.[14-20] The reason that carbon was not discernible in the intimal macrophages in these experiments, in contrast to the findings of Lausche,[4] Hueper,[21] or Benacerraf,[14] is probably because of the small amounts of foreign material injected, as compared with the massive doses of these authors.

Since the reticuloendothelial cells have been shown to contain lipid in those animals made hypercholesteremic, it may be hypothesized that the function of the reticuloendothelial system is altered in the same manner by high cholesterol content and by

particulate substances, such as carbon or Thorotrast. Presuming this be true, the pathogenesis of the vascular lesions produced in this series of experiments appears to be identical with that produced in rabbits by induced hypercholesteremia. The common factor in either instance involves an interference with the normal functions of the reticuloendothelial system.

Summary

The intravenous injection of a colloidal suspension of carbon (India ink) into rabbits resulted in producing a prolonged hypocholesteremia as well as intimal changes resembling atherosclerosis in the pulmonary and coronary arteries. Lipid was not demonstrable in these arterial lesions as long as the animals remained hypocholesteremic, but five days after cholesterol was added to their diet lipid was demonstrated. It is hypothesized that the pathogenesis involved in this series of experiments is related to interference in the normal functions of the reticuloendothelial system, and that the same mechanisms may be involved in the production of atheromata in rabbits by induced hypercholesteremia.

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Radiation Effects of Neutron-Capture Therapy on a Malignant Vascular Neoplasm of the Cerebellum

Histopathological Observations

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This report presents the histopathological findings in biopsy tissues from a malignant vascular neoplasm arising in the cerebellum of an 11-year-old child. The biopsy specimens were taken before and at intervals up to 92 days after neutron-capture therapy. This is the first time that a neoplasm of this type has been subjected to this experimental clinical procedure. The radiation effects upon the neoplasm were striking and produced a dramatic clinical response. In this procedure the patient is given an intravenous injection of sodium pentaborate, followed at a predetermined, but short, interval by an exposure to tissue infiltration by thermal neutrons from the Brookhaven Graphite Research Reactor. Following the capture of a thermal neutron by the boron-10 atom, the latter promptly disintegrates into an alpha particle and an energetic lithium atom, with a large release of energy (2.4 mev). All the energy of the alpha particle and the lithium atom are absorbed within a tissue volume approximately that of one cell. Highly localized lethal cytological effects may thereby be attained.

Clinical Note

The patient was admitted in a critical condition, being in a deep coma and completely unresponsive. Nearly 11 months before a neoplasm of the right cerebellar hemisphere was found when a suboccipital craniotomy was performed. Extensive postoperative x-radiation therapy was administered but was not effective. Gradually the neoplasm grew and extended progressively from the suboccipital area to the right angle of the mandible. Despite the size of the neoplasm, its failure to respond to x-radiation, and the patient's desperate condition, neutron-capture therapy was carried out. The dose of B^{10} was given as 4.61 gm. of sodium pentaborate, while the neutron dose at the port was 2.23×10^{12} neutrons per square centimeter. Subsequently the patient's vital signs returned to normal, and within three days there was progressive softening of the neoplasm. The port employed was not large enough to allow irradiation to all of the neoplasm; so a second course of neutron-capture therapy was administered approximately 10 weeks later. Eight days later, after a coma of four and a half months, the patient regained consciousness. Three months after the second treatment (and at the time of the writing of this report) the patient was up daily in a wheel chair and showing on repeated neurological examinations a continuing return toward normality.

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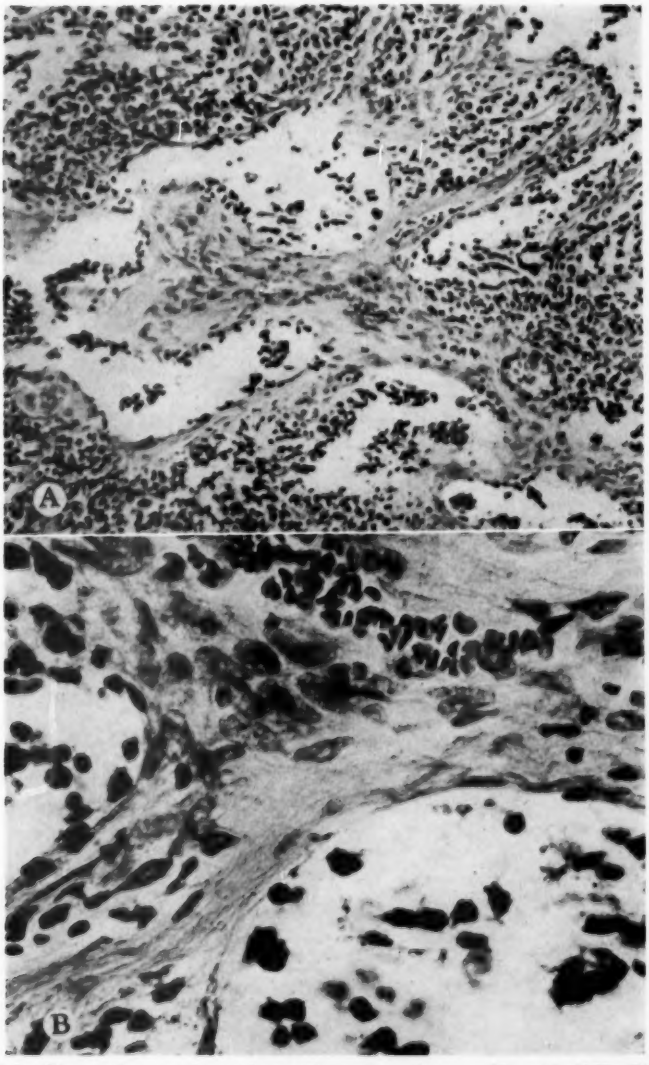
Medical Department, Brookhaven National Laboratory.

Research supported by the U.S. Atomic Energy Commission.

Histopathological Findings

The first biopsy specimen available for study was taken on Nov. 16, 1957, at the time of the craniotomy. Figures 1*A* and *B* and 2*A* and *B* are from this specimen. The cellular pattern of the neoplasm is shown in subsequent figures, while this preparation indicates the extent and arrangement of the connective tissue stroma. The denseness of the connective tissue network, which permeates irregularly throughout the entire neoplasm, is brought out by the Laidlaw stain. The cellular character of the neoplasm is seen in Figure 3*A* and *B*. There is a rather profuse proliferation of these cells, without any consistent arrangement. The neoplastic cells have oval to round prominent nuclei and scant cytoplasm. Mitotic figures are numerous and prominent.



Figs. 1-3.—Biopsy tissues taken prior to time of craniotomy, Nov. 16, 1957. Photographs from Brookhaven National Laboratory, Photography Division. All photographs reduced to ⅝ of original size.

Fig. 1.—*A*, × 100; Neg. No. 3-45-59. *B*, × 400; Neg. No. 3-43-59.

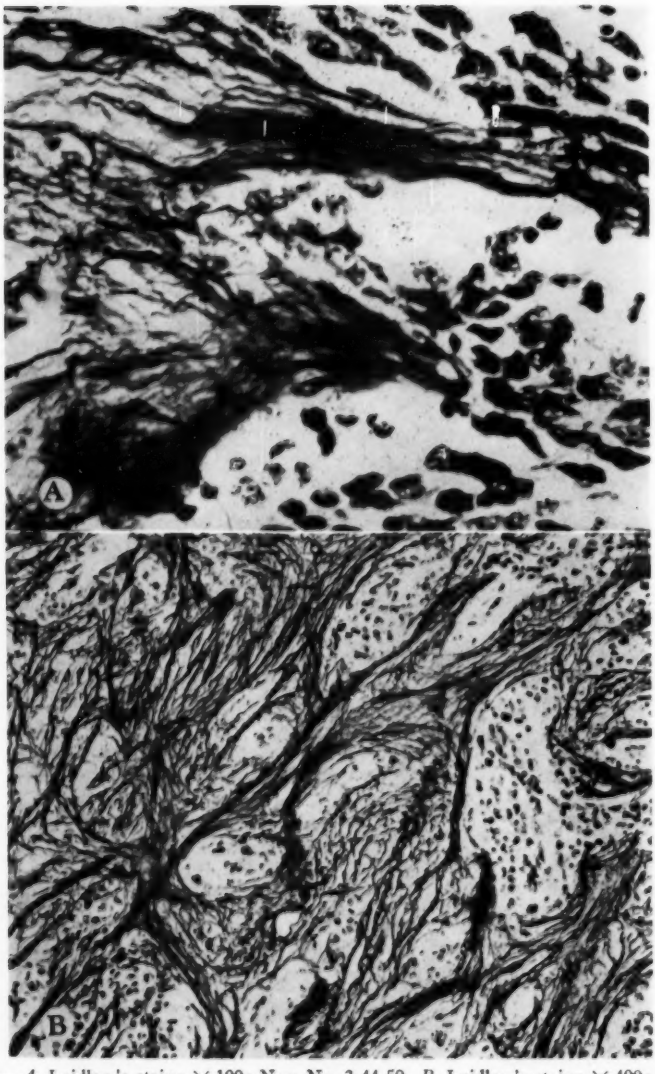


Fig. 2.—*A*, Laidlaw's stain; × 100; Neg. No. 3-44-59. *B*, Laidlaw's stain; × 400; Neg. No. 3-46-59.

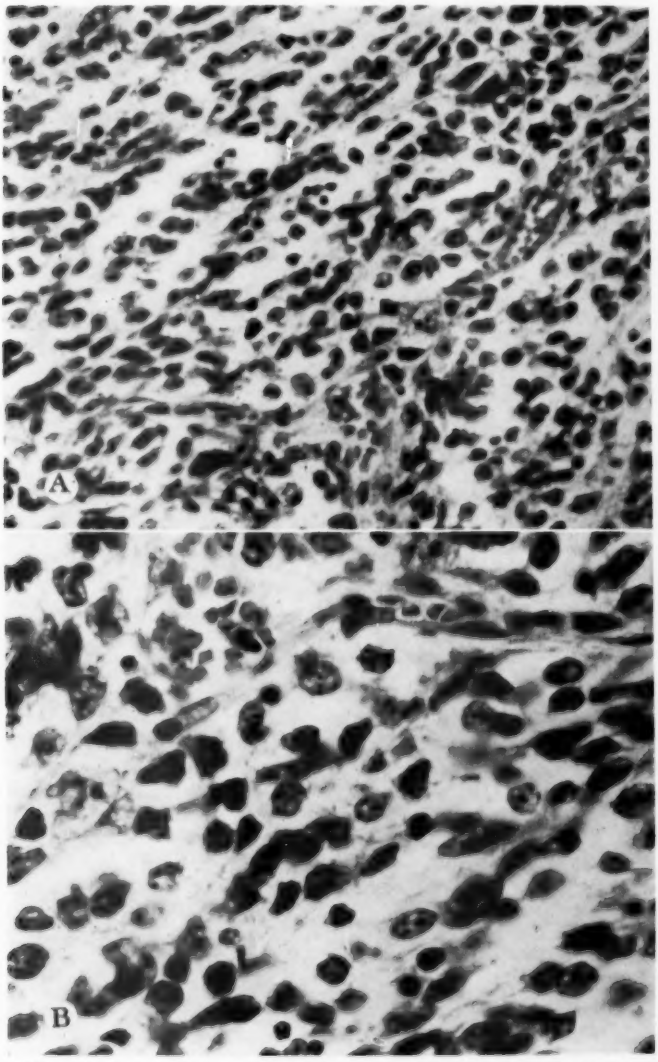
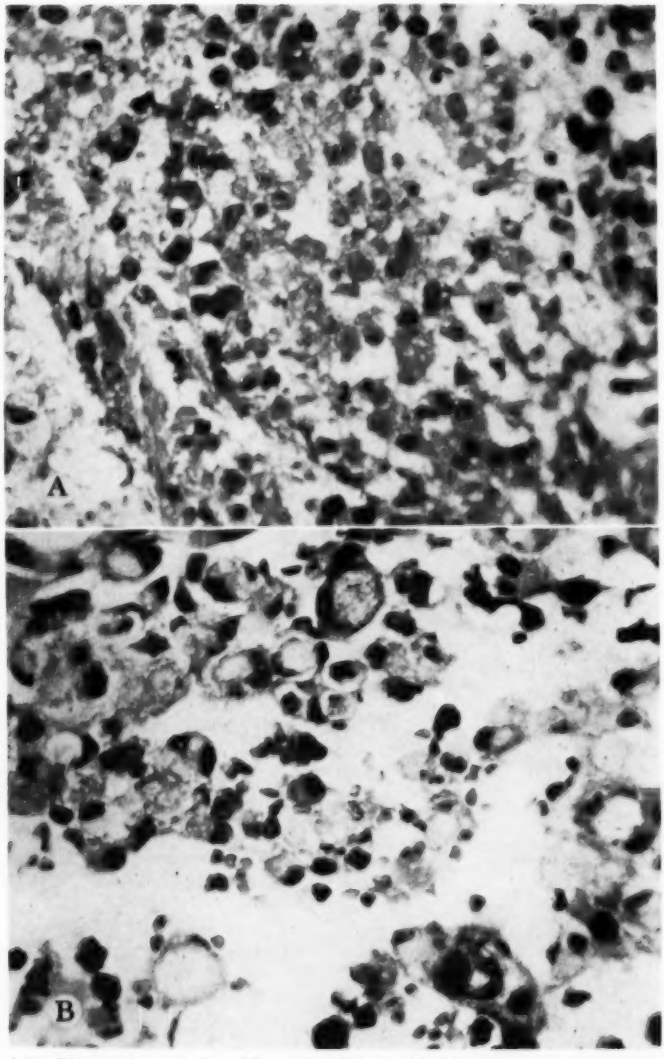


Fig. 3.—*A*, × 250; Neg. No. 12-33-58. *B*, × 480; Neg. No. 12-32-58.



Figs. 4-6.—Biopsy tissues taken Nov. 19, 1959, or 14 days after neutron-capture therapy. Photographs from Brookhaven National Laboratory, Photography Division. All photographs reduced to ⅘ of original size.

Fig. 4.—*A*, ×400; Neg. No. 12-35-58. *B*, ×400; Neg. No. 2-372-59.

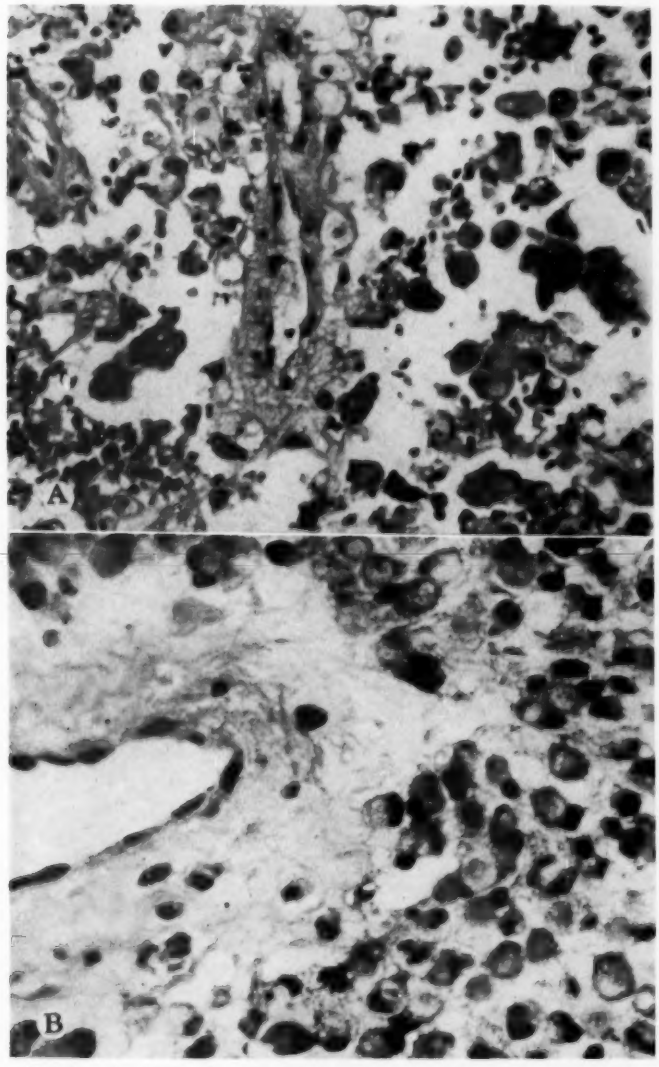


Fig. 5.—*A*, × 250; Neg. No. 12-31-58. *B*, × 400; Neg. No. 12-373-59.

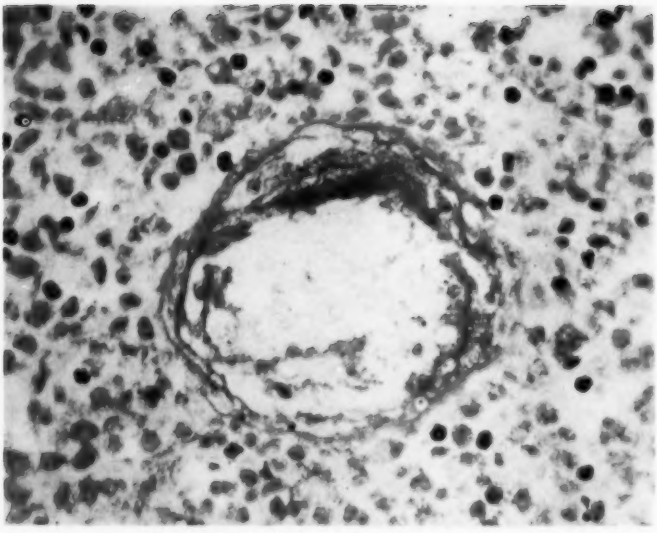
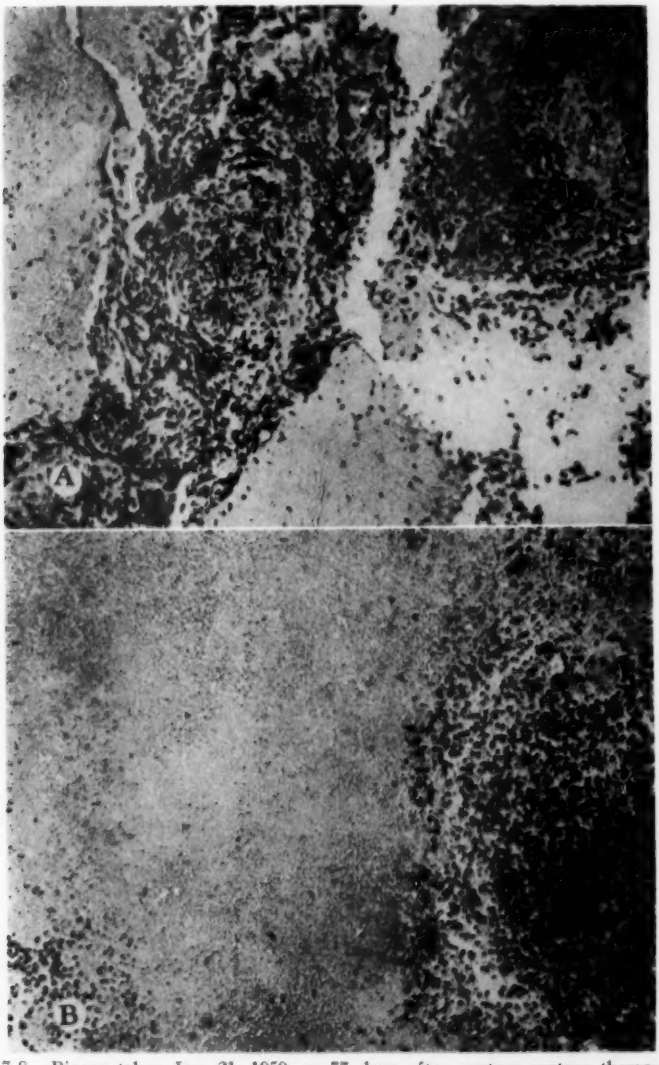


Fig. 6.—× 250; Neg. No. 2-373-59.



Figs. 7-8.—Biopsy taken Jan. 21, 1959, or 77 days after neutron-capture therapy. Photographs from Brookhaven National Laboratory, Photograph Division. All photographs reduced to 4/5 of original size.

Fig. 7.—*A*, × 100; Neg. No. 2-365-59. *B*, × 100; Neg. No. 2-366-59.

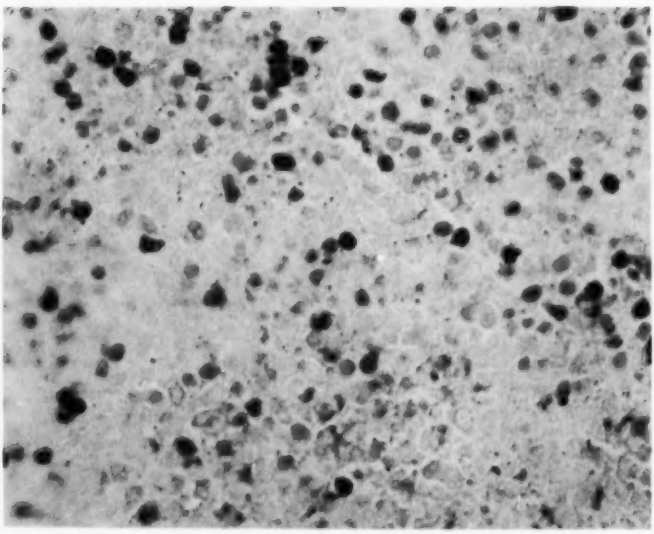


Fig. 8.—× 400; Neg. No. 2-367-59.

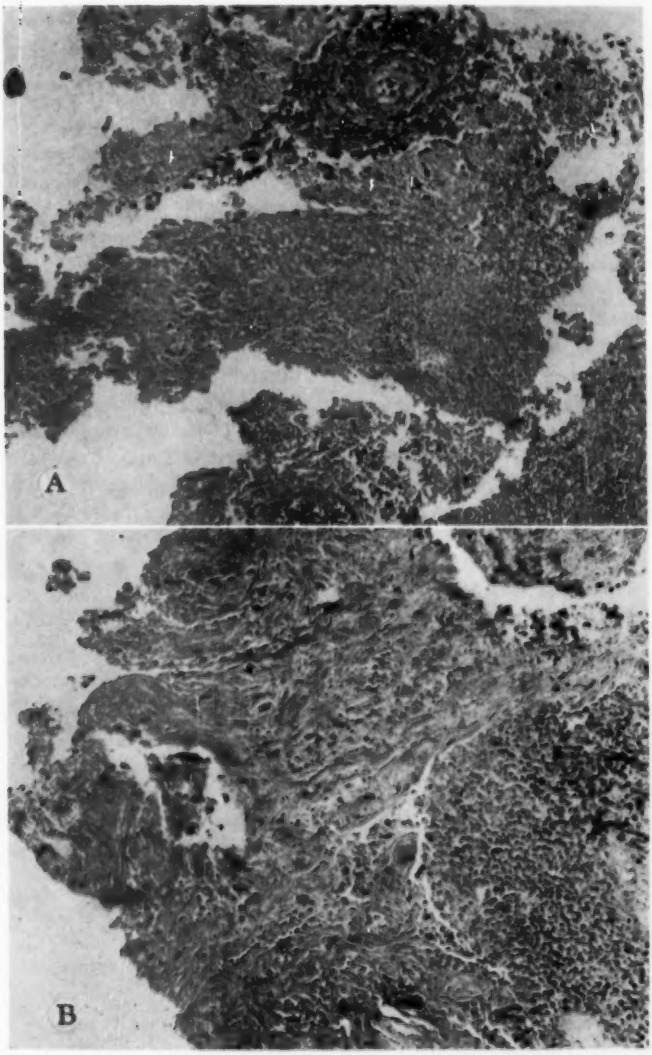


Fig. 9.—Biopsy tissue taken on Feb. 4, 1959, or 92 days after the first course of neutron-capture therapy and 14 days after the second course. Photographs from Brookhaven Laboratory, Photograph Division. Reduced to ⅘ of original size. *A*, × 500; Neg. No. 2-368-59. *B*, × 500; Neg. No. 2-369-59.

Many variable-sized vascular channels are found throughout the neoplasm.

On Nov. 19, 1958, or 14 days after neutron-capture therapy, two bits of tissue from the neoplasm were removed and examined microscopically. This tissue came from within the irradiated area and shows the widespread effect of the alpha particle radiation. In an area of what was previously composed of densely cellular, viable neoplastic cells there is apparent widespread cellular necrosis (Fig. 4*A* and *B*). A few fairly distinct nuclei remain, but most are in various stages of degeneration, and the cells are markedly ballooned out with abundant granular cytoplasm. This feature is shown more strikingly in the perivascular necrotic neoplastic cells in Figure 5*A* and *B*. Necrosis of a small artery, as well as neoplastic cells, is seen in Figure 6.

Seventy-seven days after neutron-capture therapy, on Jan. 21, 1959, another biopsy specimen was taken outside the port of irradiation. However, necrosis was present in this section in many parts of the neoplasm, although solid islands of viable neoplastic cells were still present (Fig. 7*A* and *B*). In Figure 8 the character of the cytonecrosis is demonstrated. Because of these areas of remaining neoplasm, a second course of neutron-capture therapy was given 78 days after the first course, and 14 days later a biopsy specimen was taken through the irradiated area. Again, small islands of neoplastic cells are seen (Fig. 9*A* and *B*) among great masses of necrotic neoplastic cells.

Summary

The direct irradiation effects on tissue from energetic heavy particles (alpha and lithium) following neutron-capture therapy are presented in studies of biopsy tissues on an 11-year-old child with a malignant vascular neoplasm of the cerebellum.

Medical Department, Brookhaven National Laboratory.

Effect of Tobacco Condensate on Respiratory Tract of White Pekin Ducks

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Several experimental studies have been made on the effects of inhalation of cigarette smoke on the respiratory tract of mice,[1-5] rats,[6] hamsters,[7] rabbits,[8] chickens, and pigeons,[8] and the effect of local applications of tobacco condensate on the mucosa of the trachea of dogs[9] and cows.[10]

We have been interested in the mechanism of removal of fluid and particulate material from the respiratory tract of white Pekin ducks.[11,12] In these studies liquid petrolatum and India ink were put into the trachea through the external larynx. It was found that these substances entered the lungs and air sacs and remained for varying periods of time. Following these experiments, we studied the effect of tobacco condensate on the respiratory tract in the duck. Tobacco condensate mixed with liquid petrolatum was put through the external larynx into the trachea of white Pekin ducks. The results are reported here.

Methods and Material

The tobacco condensate was obtained by the mechanical smoking of cigarettes and was obtained commercially.* It was shipped in 3 ml. ampules, packed in solid CO_2 (dry ice) and kept at 20 C. Three milliliters of this condensate was added to 19.0 ml. of liquid petrolatum. One-half milliliter of this mixture was put into the trachea of young adult ducks once each day except for holidays. This tobacco condensate-liquid petrolatum mixture was put into a syringe, to which a small plastic catheter was attached. The mouth of the duck was manually opened; and when the external larynx spontaneously opened, the catheter was inserted into the trachea for a distance of 2-6 cm. Five to ten minutes following an intratracheal injection some of these birds began to show a generalized tremor, accompanied by an increased respiratory rate. This reaction was most pronounced when the injections were resumed after an interval of several days; however, it was not necessary at any time to discontinue the intratracheal injections of the tobacco condensate because of this nicotine-like reaction.

All ducks were kept either in small batteries in the animal room or in a large outside pen with other ducks. Food and water were available at all times. The tracheas from 99 normal ducks and from 26 ducks given intratracheal injections of liquid petrolatum were studied histologically. Seven ducks in the latter group were given a total of 7 to 12 injections of 0.5 ml. each and were killed immediately after the last injection; seven were given 7 to 12 injections and were killed 24 hours after the last; two were given 15 injections and were killed 18 days later; two were given 115 injections and were killed 24 hours later; three were given 130 injections within a period of 190 days and were killed 24 hours after the last injection; five were given 15 injections and were killed 266 days after the last.

Twenty-six ducks were given the tobacco condensate intratracheally. Seven were given one injection, and five of these were killed 5 to 15 minutes later; one was killed after 24 hours and one after 63 hours. Ten ducks were given 10 injections within a period of 13 days and were killed on the 22d and 23d days following the first injection. Nine ducks were given a total of 130 injections within a period of 190 days. Two of these ducks died on the 208th and 268th days following the first intratracheal injection. Two were killed 191 days after the first injection; one on the 369th day, and four on the 721st day after the first intratracheal injection of the tobacco condensate. The respiratory tract was examined grossly in all ducks, and three sections were removed for

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Professor of Pathology, University of Texas Medical Branch.

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* Details referable to the production of this preparation may be obtained from the Tobacco Industry Research Committee, 150 E. 42d St. New York 17.

histologic study from the upper, middle, and lower thirds of the trachea and from the lungs of a majority of the birds. These were fixed in a 4.0% solution of formaldehyde. Paraffin sections were prepared and stained routinely with hematoxylin and eosin. Osmic acid and periodic acid-Schiff stains were made on select tissues.

The respiratory tract after removal was examined macroscopically for fluorescence, using an ultraviolet light (Aloe: No. 52140 ultraviolet, Mineralight, high-intensity, long-wave 3,660 A.). Some of the specimens were observed for fluorescence after they had been fixed in formaldehyde.

Experimental Results

Seven ducks were given a single intratracheal injection of the tobacco condensate and liquid petrolatum, and five were killed 5 to 15 minutes later. The mucosal surfaces of the trachea and larger bronchi were discolored. These areas fluoresced under ultraviolet light. One duck was killed after 24 hours, and only a few focal areas in the trachea fluoresced. Another bird, killed after 63 hours, also showed only a few areas that fluoresced. This experiment was repeated in 10 ducks. However, these ducks were given 10 intratracheal injections of the tobacco condensate and were killed on the 22d and 23d days following the first injection. There was no fluorescence in the trachea of any of these birds; however, in four there were focal areas of fluorescence at the periphery of either one or both lungs (not in the air sacs). These areas of fluorescence in the periphery of the lungs seemed to occur in focal areas of acute and chronic inflammation. Fluorescence was present in the trachea of a duck treated with tobacco condensate for 130 times and killed 24 hours after the last treatment. Two ducks that were treated an equal number of times and died on the 15th and 76th days, respectively, after the last injection did not show any fluorescence in the respiratory tract.

These observations show that tobacco condensate following an intratracheal injection does enter the trachea and lungs and that it persists macroscopically for at least 24 hours, as shown by ultraviolet fluorescence. In Figure 1*D* there is a localized area of yellowish-brown lipid material in the wall of the lesser abdominal air sac. This duck was given 10 intratracheal injections of tobacco condensate and was killed 10 days following the last. An acute and chronic reaction is associated with this collection of liquid petrolatum and tobacco condensate. In the periphery of the lung of

Fig. 1 (Duck 1391).—A collection of the tobacco condensate-liquid petroleum mixture on the wall of the abdominal air sac.

A, lung; *B*, liver; *C*, heart, and *D*, lesser abdominal air sac. This bird was given 10 intratracheal injections of the tobacco condensate-liquid petrolatum mixture and was killed 10 days after the last.

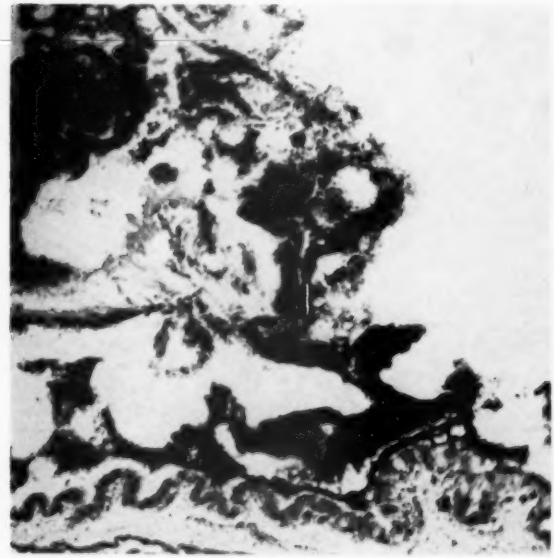

Fig. 2 (Duck 1291).—The tobacco condensate-liquid petrolatum mixture in the lumen of a bronchus. This duck was given 130 intratracheal injections and was killed 24 hours following the last. Osmic acid stain; × 120.

this duck was a localized area of chronic inflammation in which there was a yellowish-brown particulate material. This area fluoresced under ultraviolet light; however, the area in the air sac failed to fluoresce. Three of ten ducks similarly treated showed foci of inflammation in the periphery of the lung that did fluoresce.

Acute and chronic inflammation of the mucosa of the trachea was found frequently in the 99 untreated ducks. Three of these showed metaplasia. Acute and chronic inflammation was present in the trachea of a majority of birds given the liquid petrolatum. Three of these birds also showed metaplasia; one of these was given 12 in-

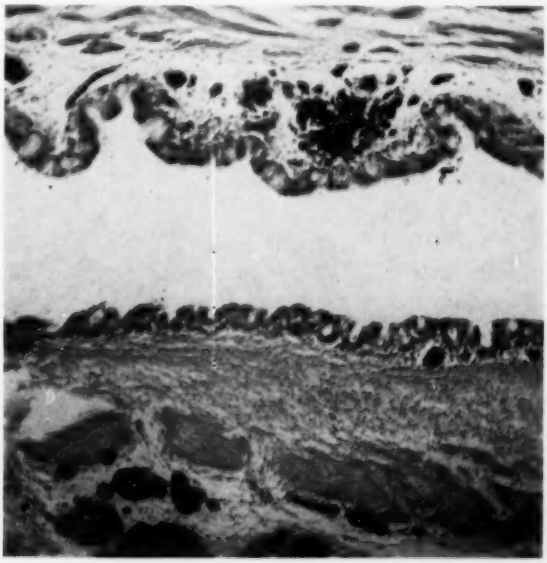

Fig. 3 (Duck 1291).—The tobacco condensate-liquid petrolatum mixture in the wall of a bronchus. Same duck as that shown in Figure 2. Osmic acid stain; × 120.

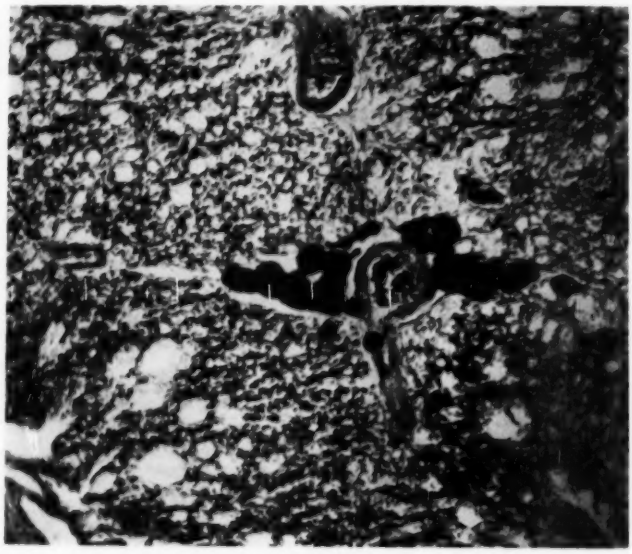

Fig. 4 (Duck 1291).—The tobacco condensate-liquid petrolatum mixture in the lumen of channels apparently lymphatic between the lobules of lung tissue. Osmic acid stain; × 110.

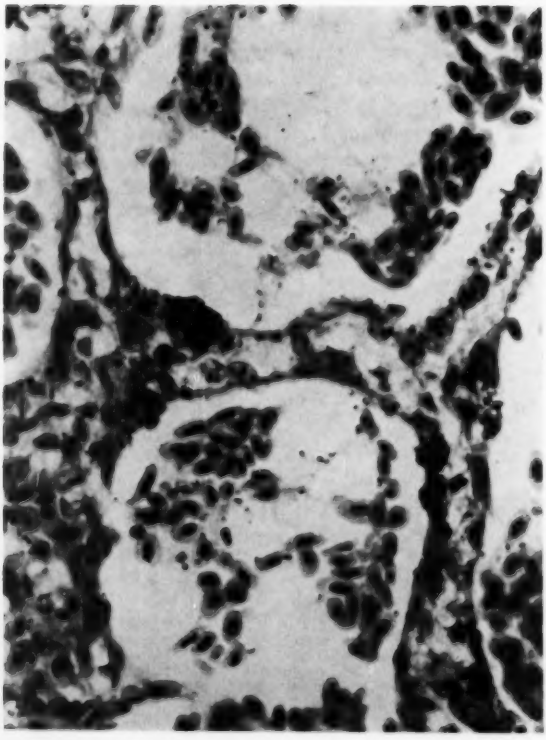

Fig. 5 (Duck 1392).—Particles of the tobacco condensate-liquid petrolatum mixture in the lumen of the air capillaries, their walls, and in the underlying stroma. Hematoxylin-eosin stain; × 617.

jections and was killed immediately after the last; one was given 8 injections and was killed 24 hours later, and one was given 15 injections and was killed 266 days later.

The trachea and lungs of the majority of the ducks given the tobacco condensate-liquid petrolatum mixture intratracheally also showed either an acute or a chronic reaction in the trachea. The cilia were absent in focal areas in the trachea and larger bronchi of some of these ducks, as well as in the controls. Many of the birds showed a varying number of lymphocytes in the wall of the trachea.

The tobacco condensate-liquid petrolatum mixture was easily demonstrated with the osmic acid stain within the lumen of the respiratory tract (Fig. 2). Lipid material also was present in the submucosa of the larger bronchi (Fig. 3) and in the lumen of either the lymphatics or the blood vessels within the lung (Fig. 4). Particles of black-staining material were present within the lumen of the air sacs (Fig. 5) and in their walls. Some of the particles were present in the fibrous tissue stroma beneath the epithelial cells lining the respiratory tract. Macrophages filled with lipid-staining material were present in the lung about the foci of acute and chronic inflammation (Fig. 6). In one of these areas there was a proliferation of fibrous tissue in which there were many foci of calcification (Fig. 7).

With the lapse of time following an intratracheal injection of tobacco condensate, groups of lymphocytes developed in the lungs and in the wall of the smaller bronchi. In these collections of lymphocytes there were varying numbers of particles of debris from the condensate (Fig. 8).

Collections of lipid material were present in the air sacs of three of the group of nine ducks given 130 intratracheal injections of the tobacco condensate. Each of the nine birds showed particles of black-staining

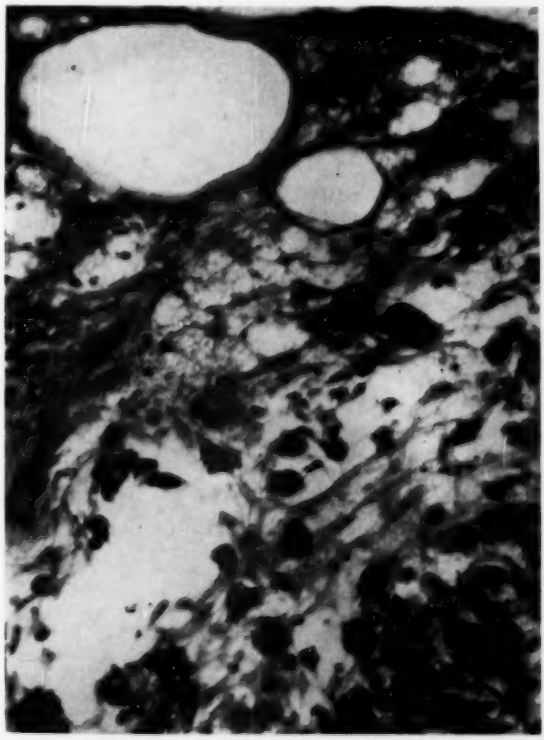

Fig. 6 (Duck 1301).—Macrophages filled with the tobacco condensate-liquid petrolatum mixture. Foci of inflammation sometimes develop in the respiratory tract after the intratracheal injections of the condensate. Osmic acid stain; × 380.

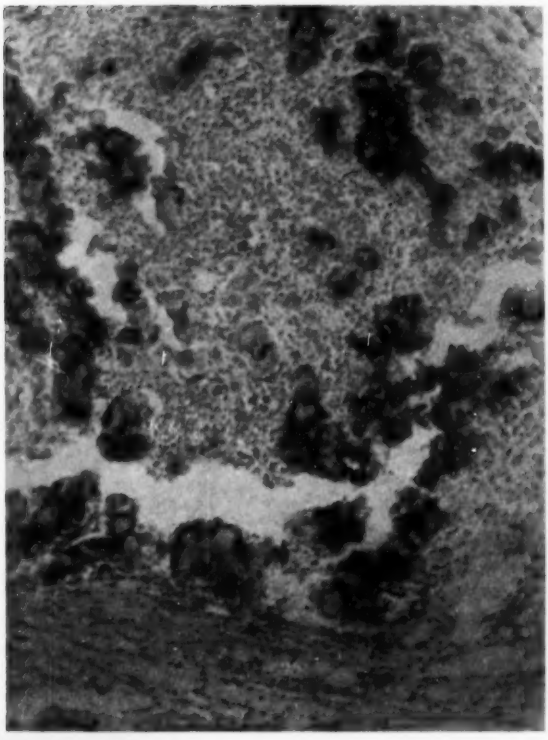

Fig. 7 (Duck 1385).—Foci of calcification sometimes are present in the areas of chronic inflammation in the lung that develop after the intratracheal injection of the condensate. Hematoxylin-eosin stain; × 120.

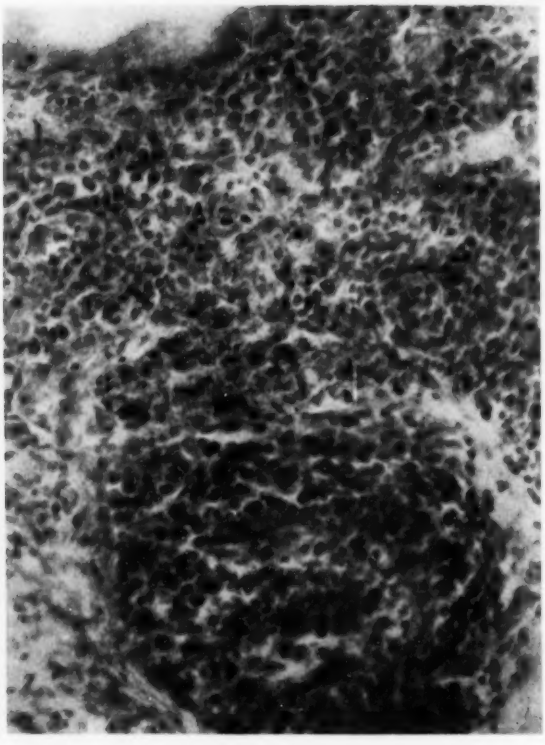

Fig. 8 (Duck 1301).—Particles from the tobacco condensate-liquid petrolatum mixture in the lymphoid tissue in the area of a large bronchus. This duck was given 130 intratracheal injections and was killed on the 369th day after the first injection. Hematoxylin-eosin stain; × 380.

Fig. 9 (Duck 1303).—The liver is approximately twice the normal size (weight, 183 gm.). This bird received the same amount of the tobacco condensate as the duck shown in Figure 8 and was killed on the 721st day following the first injection.

material, considered to be from the tobacco condensate in the lymphoid tissue about the wall of the larger bronchi (Fig. 8). There were no pathologic changes observed in the trachea of six of these ducks given 130 intratracheal injections. In three there were either a few leukocytes or lymphocytes or both. No metaplasia occurred in the trachea, and no significant pathologic lesions were observed in the lungs and air sacs.

The liver was cirrhotic in three of the nine ducks given 130 intratracheal injections of the condensate. One of these ducks died on the 208th day after the first intratracheal injection, and the other two birds were killed on the 721st day. The cirrhotic livers usually were approximately twice the size of the normal. Ascitic fluid was present in two of these birds. The typical hepatic lesion is shown in Figures 9 and 10. In some of the specimens the greater portion of the liver was involved; however, in others less of the parenchyma was affected. The involved areas of liver were yellowish-brown in color and firm in consistency. The color and consistency of the liver were typical of amyloid. The hepatic cells were completely destroyed in some areas, while in others a few distorted hepatic cells were still present (Fig. 10). The infiltrating material was pink-staining and homogeneous in the hematoxylin-and-eosin preparation. It was red following the staining of the tissue with the periodic acid-Schiff reaction. This amyloid-like material,

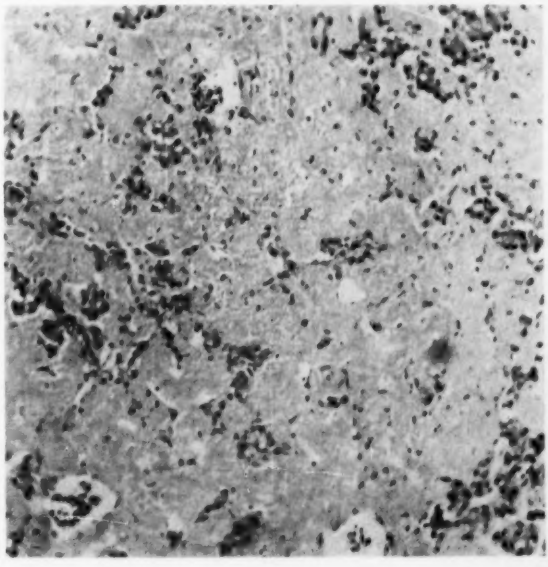

Fig. 10 (Duck 1303).—The scarring in the liver results from an infiltration of the areas with an amyloid-like material. In many areas the hepatic cells are completely replaced by this substance. The same liver as shown in Figure 9. Hematoxylin-eosin stain; × 130.

however, failed to stain with crystal violet. There was no significant inflammatory reaction within these cirrhotic livers.

Comment

The anatomical distribution of the particles in this preparation of tobacco condensate and the globules of petrolatum put into the trachea of these ducks is the same as that observed in previous studies using India ink and liquid petrolatum.[12] These particles also enter the lymphatics and blood vessels as do the particles of liquid petrolatum. The inflammatory reaction resulting from the instillation of tobacco condensate in liquid petrolatum into the trachea of ducks is no different from that observed with liquid petrolatum alone. In the group of 99 normal ducks acute and chronic tracheitis was observed frequently. Metaplasia was present in 3 of 26 ducks injected with liquid petrolatum only. Extreme care, therefore, must be used in the interpretation of inflammation and metaplasia in the trachea of ducks following the intratracheal injection of any agent.

There was nothing in these experiments to suggest carcinogenic action of the tobacco condensate in the respiratory tract. Obviously, these birds had an opportunity to react to such an agent, since fluorescence persisted in the trachea and in the lungs for at least 24 hours following a single intratracheal injection of the condensate. Furthermore, the ducks did absorb the nicotine that was present, as indicated by their tremor and increase in the respiratory rate. Two of the nine ducks given 130 intratracheal injections were observed for 191 days, one for 208 days, one for 268 days, one for 369 days, and four for 721 days, after the first intratracheal injection of the tobacco condensate. Of course, one may conclude that the number of ducks is too few, the length of time is too short, and the amount of condensate is too small, to produce neoplastic changes. Such may be true; however, apparently no one has produced neoplasia in the respiratory tract of experimental animals, either by inhalation of cigarette smoke or by the local application of tobacco condensate to the mucosa[6,13]; so we have no basis at the present for a quantitative estimation of either the amount of condensate necessary or the length of time required for development of neoplasia. Essenberg[2] and Campbell[1] obtained tumors in mice which they thought resulted from the inhalation of cigarette smoke.

In the trachea of the duck one must be careful in assuming a specific relation between metaplasia and neoplasia. In the dog, tobacco condensate, when applied to the tracheal mucosa, was remarkably effective in inducing metaplastic changes in the mucosa; however, no atypicality was noted, and nothing suggestive of the so-called precancerous alterations was observed by Rockey and associates.[9]

One of the most interesting pathologic changes observed in this study is the cirrhosis found in three ducks given the tobacco condensate for the longest periods. The morphologic and histochemical changes in the liver are suggestive of amyloidosis. An identical process has been observed in ducks receiving methylcholanthrene.[14] This observation would suggest that something is present in tobacco condensate that reacts with some substance present in the reticulum in the liver that forms an amyloid-like substance. In the duck this amyloid-like material apparently is a mucoprotein, since it gives a positive reaction with the periodic acid-Schiff stain. In the statistical studies in man, cigarette smoking has been associated with everything but amyloidosis. It is of considerable interest, therefore, to find amyloidosis associated with tobacco condensate in the duck.

Summary

Tobacco condensate obtained by the mechanical smoking of cigarettes was mixed with liquid petrolatum and put into the trachea of white Pekin ducks through the external larynx. Either this material was phagocytosed, or it passed between the epithelial cells lining the respiratory tract to

reach the adjacent stroma, and subsequently it entered the lymphatics and blood vessels. An acute and chronic reaction occurred in the trachea of a few of the birds. A similar reaction, however, was present in normal birds and in some of those receiving only the liquid petrolatum. Therefore, the significance of this reaction is difficult to evaluate. Nine ducks given 130 intratracheal injections of the condensate were observed from 191 to 721 days following the first injection. There is nothing in this study to suggest neoplasia. Amyloid-like material occurred in the liver of three of the nine ducks given the tobacco condensate.

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Adenocarcinoma Arising in Presacral Enterogenous Cyst

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Enterogenous cysts, or duplications of the alimentary tract, are uncommon developmental anomalies. They generally produce symptoms due to encroachment on adjacent viscera. They may be associated with any portion of the gastrointestinal tract but are most frequently encountered in the ileocecal region.[1] Occasionally, they are found in the sacrococcygeal region, probably derived from persisting remnants of postanal gut.[2] In this latter location, they are sometimes referred to as postanal gut cysts.

Adenocarcinoma arising in a presacral enterogenous cyst is extremely rare. A well-documented case has been described by Ballantyne,[3] who reviewed the early literature on this subject. This report describes an additional example of adenocarcinoma arising in a presacral enterogenous cyst in a 37-year-old woman.

Submitted for publication April 30, 1959.

We wish to thank Dr. Raffaele Lattes for examining sections from this case, and for confirming the identity of this tumor.

From the Department of Pathology and Surgery, the University of Vermont College of Medicine, and the Mary Fletcher Hospital.

Report of a Case

The patient was a 37-year-old white woman who was admitted to the hospital in January, 1958, complaining of back pain. Rectal examination revealed a fixed, firm, and nontender mass encroaching on the posterior rectal wall. Sigmoidoscopy revealed a protrusion of the rectal wall but no apparent involvement of the mucosa. X-ray examination of the pelvis revealed a partially calcified mass anterior to the sacrum without evidence of bone erosion (Fig. 1). On intravenous pyelography, the mass appeared to indent the bladder slightly.

An operation was performed under spinal anesthesia with the patient in the prone position. A small circumscribed precoccygeal mass was encountered and removed, together with the coccyx. A second large circular mass, measuring about 5 cm. in diameter, was encountered in the presacral

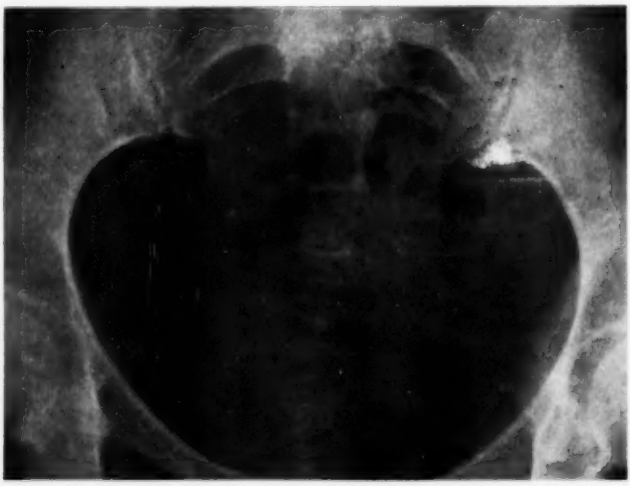

Fig. 1.—Radiograph of pelvis demonstrating calcified presacral mass.

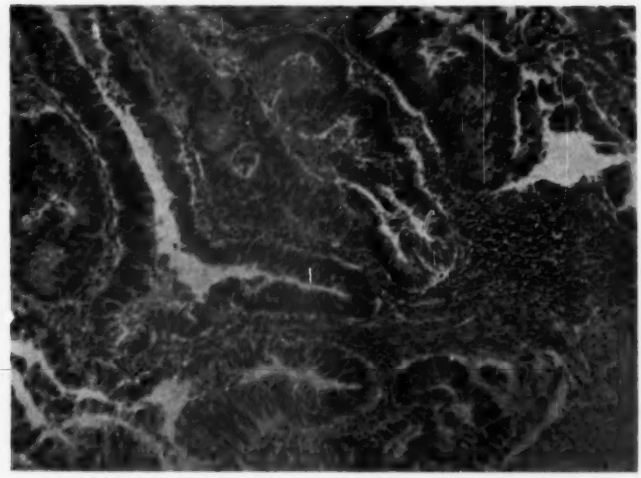

Fig. 2.—Photomicrograph of mucin-secreting adenocarcinoma invading wall of cyst. Hematoxylin-eosin stain; × 400.

area. Dissection was carried anteriorly between the mass and the bowel wall, and no attachment to the bowel was detected. The dissection was then carried posteriorly, where the neoplasm appeared adherent to the sacrum. During the dissection, the larger cystic lesion was ruptured.

The surgical specimens consisted of two cystic structures. Both lesions appeared well encapsulated. The smaller precoccygeal cyst measured 1 cm. in diameter, had a thin wall, measuring about 0.1 cm. in thickness, and was adherent to the inner surface of the coccyx. Histologically, this lesion was an epidermal cyst. The larger presacral cyst measured 5 cm. in diameter. The wall was 1.5 cm. in thickness, and its internal surface was covered by brown granular material.

Histologically, most sections revealed a moderately well-differentiated, mucin-secreting adenocarcinoma arising from the mucosa and invading the cyst wall deeply, but not infiltrating the full thickness of the wall (Fig. 2). In a few sections remnants of mucosa which were not involved by carcinoma could be identified. In these areas the lining epithelium consisted of columnar epithelial cells, which in some areas showed mucin secretion; the subepithelial tissues showed marked fibrosis and focal accumulations of chronic inflammatory cells (Fig. 3). In several areas there was heavy deposi-

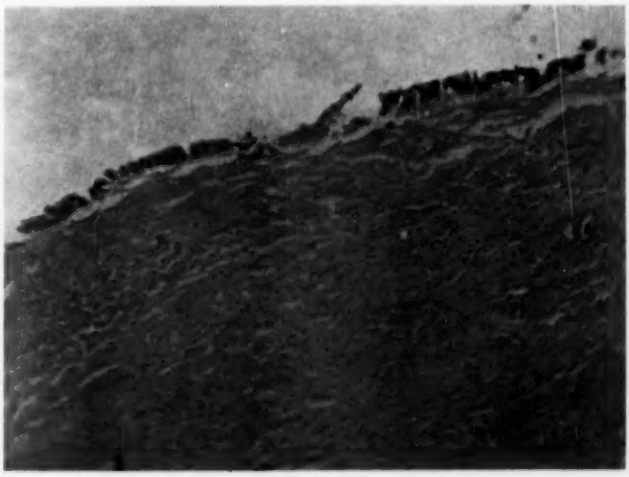

Fig. 3.—Photomicrograph of a portion of cyst uninvolved by carcinoma, illustrating columnar epithelial lining and submucosal fibrosis. Hematoxylin-eosin stain; × 400.

tion of calcium in the wall. All sections of the wall showed a double layer of smooth muscle, characteristic of gastrointestinal tract. The lesion was interpreted as an invasive adenocarcinoma arising in a presacral enterogenous cyst. Ten days after the excision of the presacral tumor, a lymphadenectomy of the hypogastric and iliac vessels were performed, and no metastatic tumor was identified in seven lymph nodes obtained from this dissection.

The patient was readmitted to the hospital in October, 1958, with symptoms suggestive of recurrent tumor. A course of palliative radiotherapy was given, without significant benefit. In January, 1959, a perineal needle biopsy revealed infiltrating adenocarcinoma in presacral tissues. A chordotomy was subsequently required for relief of pain.

Comment

The cystic presacral lesion was completely independent of the rectal wall but had the typical structure of gastrointestinal tract and fulfills the criteria of an enterogenous cyst of developmental origin. The heavy calcification of the wall, demonstrable both histologically and radiologically, also suggested that the cyst had been present for a considerable period before carcinoma developed. Although the development of carcinoma in an enterogenous cyst is rare, this possibility should be considered when dealing with lesions of this nature. In this case, the carcinoma had not as yet invaded the full thickness of the cyst wall, and it is possible that rupture of this enterogenous cyst incident to removal may have been a factor leading to the recurrence.

Summary

A case of invasive adenocarcinoma arising in a presacral enterogenous cyst is presented. Presacral enterogenous cysts are uncommon developmental anomalies, resulting from persisting remnants of postanal gut. Although carcinoma supervening in an enterogenous cyst is rare, this possibility should be considered when dealing with developmental lesions of this nature.

University of Vermont College of Medicine.

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Capillaries of Normal and Diseased Breast

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Introduction

Nonspecific alkaline phosphomonoesterase * is present in endothelial cells of capillaries in breast.[1-4] This can be demonstrated histochemically by a colored precipitate at the sites of reaction. Montagna and Ellis have demonstrated long segments of capillaries in skin by staining thick sections of tissue.[5,6] We have used this technique to study the capillary vasculature of normal breast, fibrocystic disease including adenosis, fibroadenoma, gynecomastia, intraductal papilloma, and adenocarcinoma. We shall subsequently report on capillaries in diseases of the heart and uterus.

Materials and Methods

This report is based on the examination of 125 specimens of breast tissue obtained from surgical biopsies or from cadavers of patients dead less than six hours. The method of handling these tissues has been described by Fanger and Barker.[3] Frozen sections of 70μ-250μ were used. The alkaline phosphatase method of Gomori, using sodium α-naphthyl acid phosphate as the substrate and diazo blue B as the dye, was most useful.[7] After 30 minutes incubation, the sections were washed for 15 minutes, dehydrated in baths of 95% and absolute alcohol, cleared in xylol, and mounted in balsam. Sections handled by this method show as much activity as those mounted in glycerin jelly. In addition, sections mounted in balsam are permanently prepared, do not bubble, and do not fade. The Lepehne-Pickworth method for hemoglobin peroxidase was used to demonstrate blood vessels by staining red blood cells.[8] Tissues must be put fresh into formalin and fixed for at least one week before cutting frozen sections. Sections were counterstained with carmalum.

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From the Pathology Department of the Rhode Island Hospital.

This investigation was supported by Research Grant CY-2926 C2 Path., from the U.S. Public Health Service.

* For brevity, the term "phosphomonoesterase" is shortened to "phosphatase."

Observations

Normal Breast.—The afferent and terminal ducts are surrounded by a network of capillaries (Fig. 1). Although the capillaries branch many times, there are few anastomoses. The network is formed by vessels which arise in the interlobular tissue, approach the duct, and then branch repeat-

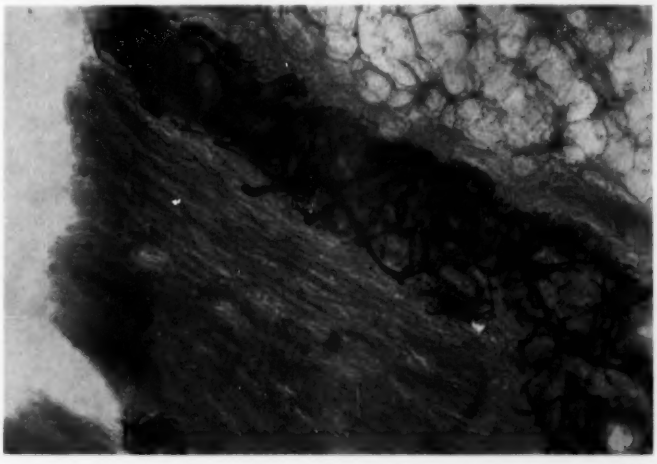

Fig. 1.—Normal breast. Network of capillaries surrounding afferent duct. Alkaline phosphatase; ×60.

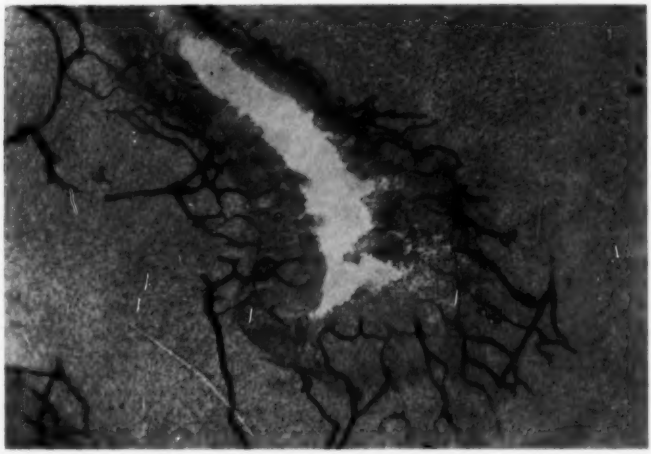

Fig. 2.—Normal breast. Capillaries originate in the stroma surrounding an afferent duct and branch as they approach the duct. Alkaline phosphatase; ×60.

edly (Fig. 2). The extension of capillaries to the ductal epithelium is not clearly demonstrated, but upon examination of many specimens one has the impression that this does occur.

Offshoots of the capillary network around the terminal ducts extend into neighboring breast lobules. This is well demonstrated in the female breast at the time of adolescence, when the breast lobules are not completely developed and the branching from the ductal system is more readily seen. In the adult female breast, a meshwork of capillaries envelops each lobule and sends multiple arborescent branches among the alveolar ducts (Fig. 3). Capillaries are rarely seen in the interlobular stroma. There are numerous capillaries in fat. Occasionally, arterioles are delineated by this technique (Fig. 9).

It has been difficult to obtain enough specimens to evaluate the effects of aging. The capillary vasculature appears to vary with the cellularity of the lobules. Capillaries

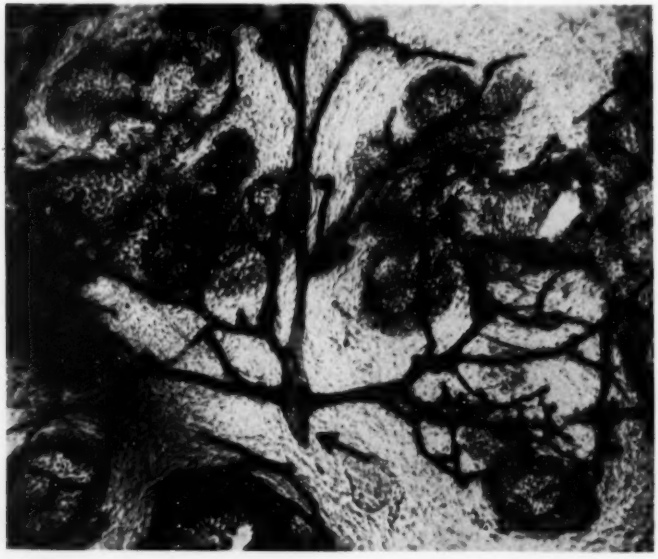

Fig. 3.—Normal breast. Multiple branching capillaries extend from an arteriole (arrow) into adjacent breast lobules. Alkaline phosphatase; ×150.

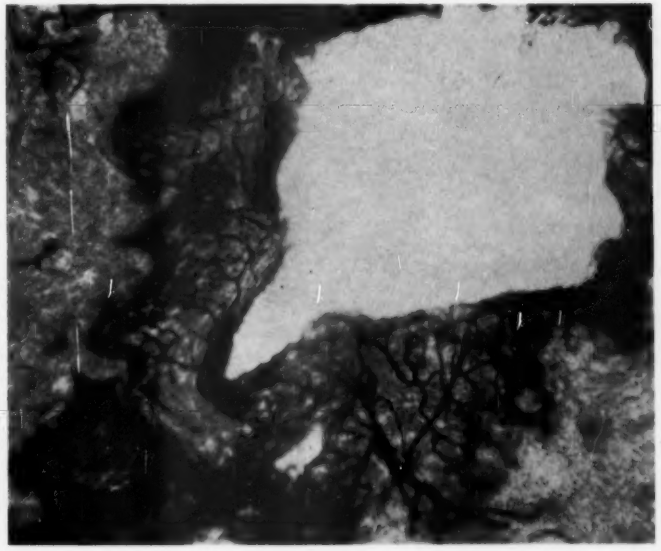

Fig. 4.—Fibrocystic disease. A network of capillaries surrounding a small cyst. Alkaline phosphatase; × 60.

were infrequently seen when the lobules were atrophic.

Fibrocystic Disease.—The lobules are larger than in normal breast, and three-dimensional visualization is difficult. A network of capillaries surrounds the lobules, entering from several sides and ramifying within them.

The small cysts are surrounded by a network of capillaries, which sends short, branching segments toward the lining epithelium (Fig. 4). The relationship between the capillaries and the epithelium is not well defined. Occasionally the capillary network seems to extend into the epithelium (Fig. 5). This is believed to be partly an artifact, due to the thick section showing epithelium and capillaries superimposed. However, there may be small capillary projections into the epithelium. This will be subsequently discussed. Short segments of capillaries are demonstrated in foci of intraductal hyperplasia. Only a few short capillary segments

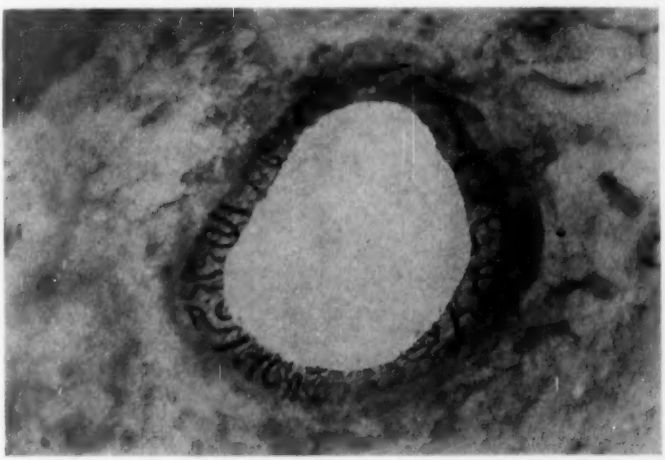

Fig. 5.—Fibrocystic disease. Capillaries in the wall of a small cyst. Alkaline phosphatase; × 60.

Fig. 6.—Fibrocystic disease. Short segments of capillaries in connective tissue surrounding a large cyst. Alkaline phosphatase; × 60.

are seen in the connective tissue surrounding large cysts (Fig. 6).

In florid adenosis capillaries are not numerous, and they branch infrequently. In sclerosing adenosis the tissue is so strongly reactive that it is not possible to see the vessels clearly (Fig. 7).

Fibroadenoma.—There are increased numbers of capillaries in close association with the numerous distorted ducts of fibroadenomas. In the areas of most marked vascularity, the capillaries ramify around and between the ducts, and it is difficult to trace them through their twists and turns (Fig. 8). The capillary vasculature is less in areas with few ducts, and the relationship of capillaries to ducts is more easily demonstrated. A fortuitous section containing branching capillaries in one plane shows them originating from an arteriole and arborizing toward the slit-like ducts (Fig. 9). In some cases there is demonstrated a relatively simple capillary network surrounding the ducts and sending small off-shoots toward them, reminiscent of capillaries around small cysts.

Gynecomastia.—The capillaries are much fewer than in fibroadenomas, but their distribution is essentially similar. They form a network around the ducts and send small branches toward the epithelium (Fig. 10). The network becomes distorted as the ducts

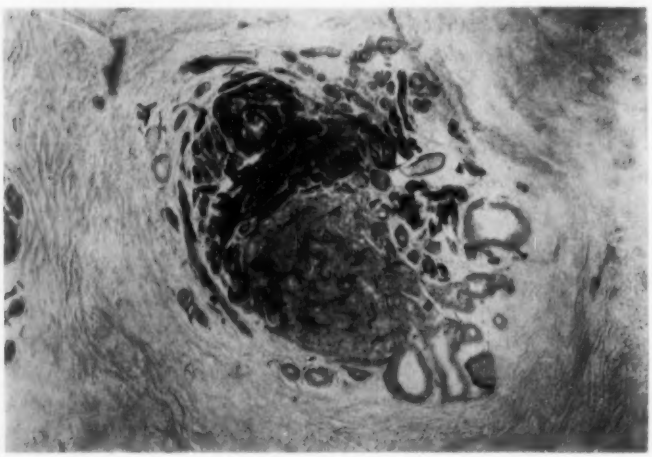

Fig. 7.—Adenosis. Short segments of capillaries delineated in the area of florid adenosis. The reactivity in the sclerosing adenosis in the upper portion of the lesion obscures the capillaries. Alkaline phosphatase; × 60.

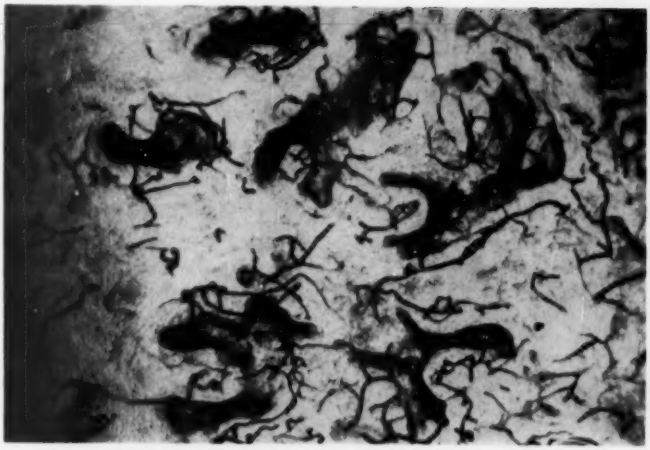

Fig. 8.—Fibroadenoma. Rich capillary vasculature ramifying around the distorted ducts. Alkaline phosphatase; × 60.

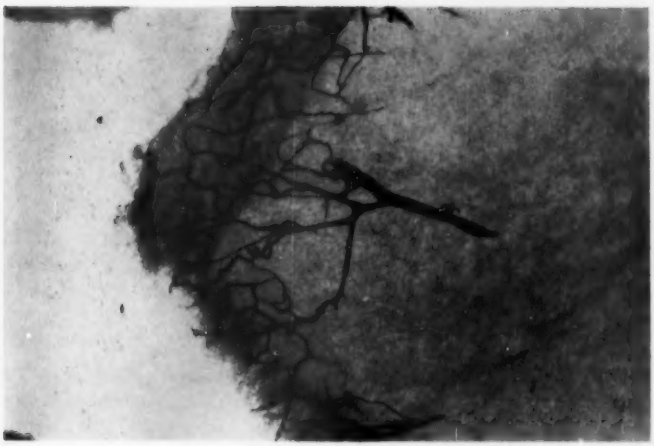

Fig. 9.—Fibroadenoma. Arteriole with multiple branching capillaries extending up to the epithelium of a duct. Alkaline phosphatase; × 60.

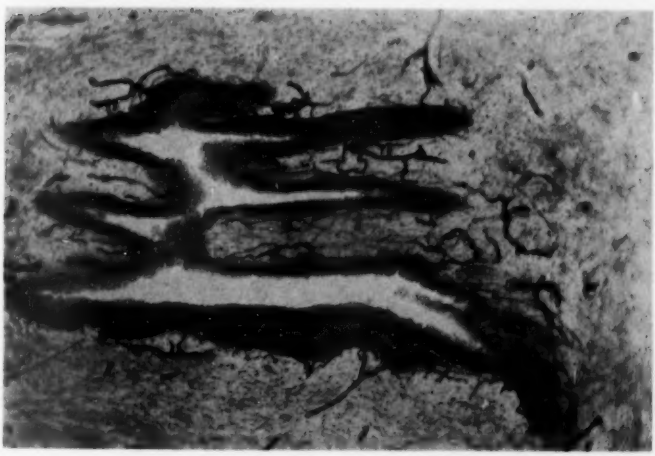

Fig. 10.—Gynecomastia. Ducts surrounded by a network of capillaries. Alkaline phosphatase; × 60.

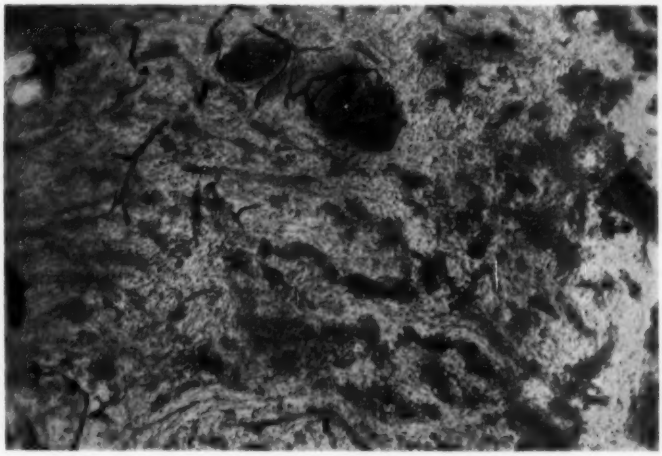

Fig. 11.—Carcinoma. Note paucity of capillaries in the stroma. A few capillary branches tend to encircle two foci of intraductal carcinoma. The cancer shows no alkaline phosphatase activity. Alkaline phosphatase; ×60.

branch or undergo cystic dilatation. The fibrous stroma between the ducts contains few capillaries, with simple, sparse branches.

Intraductal Papilloma.—The capillaries in the connective tissue cores of the papillary processes show a minimal amount of branching.

Carcinoma.—With the alkaline phosphatase technique, the capillary vasculature seems to be diminished in all types of carcinoma except in intraductal carcinoma. Occasionally, straight segments of capillaries with a few branches may be seen in the stroma adjacent to the infiltrating tumor cells (Fig. 11). There is a contrast between the capillary vasculature of uninvolved tissue at the periphery of the tumor and the capillary vasculature in the tumor (Fig. 12). Only few capillaries are demonstrated in colloid carcinoma and in scirrhus carcinoma. In intraductal carcinoma, capillaries ramify around the involved ducts, but there is a less complex branching than in benign lesions of the breast (Fig. 13). However, this feature is not constant, as shown in Figure 14, in which a striking network of capillaries encompasses a carcinomatous duct. Blood vessels were demonstrated in breast cancer with the Lepehne-Pickworth nitroprusside (nitroferrocyanide)-benzidine method (Fig. 15). This method does not delineate adequately the types of blood ves-

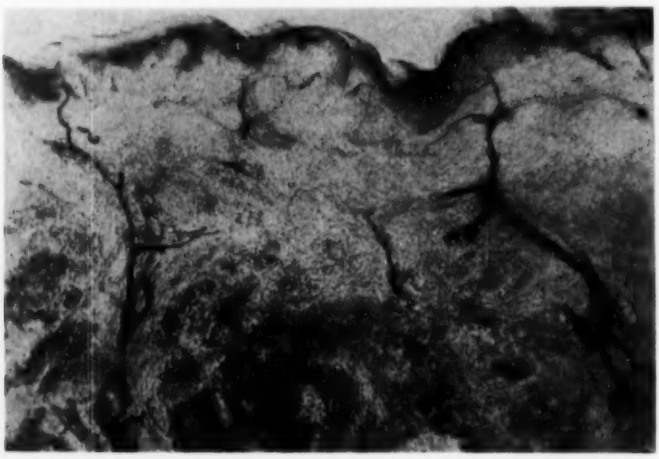

Fig. 12.—Carcinoma. Section of skin with underlying carcinoma. Note the distorted capillaries of the corium, in contrast with the rare capillary segments in the tumor. Alkaline phosphatase; ×60.

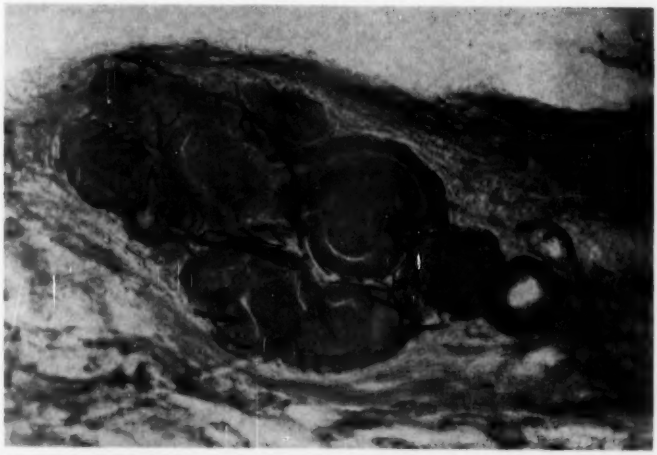

Fig. 13.—Carcinoma. Intraductal carcinoma with surrounding capillaries. Alkaline phosphatase; × 60.

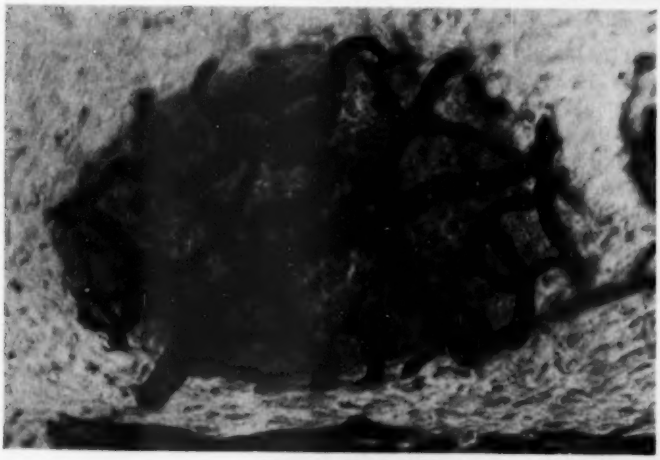

Fig. 14.—Carcinoma. Intraductal carcinoma surrounded by a rich network of capillaries. Alkaline phosphatase; × 200.

Fig. 15.—Carcinoma. Blood vessels demonstrated by means of the Lepehne-Pickworth technique. Alkaline phosphatase; reduced to 88% of mag. × 200.

sels; but, judging from the caliber of the vascular channels, some of these are capillaries.

Connective tissue stains, such as the phosphotungstic acid-hematoxylin, aniline blue, Weigert's elastic fiber and reticulum stains, were ineffective in demonstrating the capillaries.

Comment

Capillaries in living tissue have been visualized by microscopic examination of mesentery [9] or of tissue transplants in the anterior chamber of the monkey's eye [10] or in the hamster's cheek pouch.[11] Microinjection with dissection and microroentgenograms have clearly delineated the capillary vasculature and made possible an understanding of the anatomy and physiology of these small vessels.[12-14] However, the procedures are difficult and time-consuming, and require special apparatus. The demonstration of capillaries in thick sections by means of the alkaline phosphatase technique furnishes a new means for studying capillaries. Its simplicity makes it especially useful. One limitation of the procedure is the variability of the reaction, possibly because of changing cellular metabolic activity. As a result, the capillaries are not uniformly depicted, even in normal tissues. Nevertheless, by processing a number of specimens, one can visualize the capillary pattern.

Montagna and Ellis have clearly delineated the location of alkaline phosphatase activity in the endothelium of capillaries, and less frequently in arterioles.[5] In breast, arterioles appear to be more readily demonstrable. The caliber of the vessels helps to distinguish capillaries and arterioles, although occasionally the distinction is difficult.

We have demonstrated capillaries in thyroid, parathyroid, heart, gallbladder, pancreas, stomach, small intestine, colon, spleen, kidney, uterus, and ovary, as well as in skin and breast, by this method. However, this procedure is not successful in demonstrating capillaries in all tissues, such as those in the liver and lung; very few are seen in the spleen.

In the normal breast this technique has demonstrated a profusion of capillaries in close association with the ducts and lobules. There is a relative paucity of demonstrable capillaries in the interlobular connective tissue. In the benign neoplasms of the breast there is distortion of the capillary pattern, corresponding to the distortion of the epithelial structures. Thus, in fibrocystic disease the small cysts are surrounded by a capillary network which has been altered, as a result of the duct dilatation. The branching capillaries surround the cysts, and in the thick sections the capillaries appear in the epithelial lining, but this may be due to an artifact. As a segment of a duct dilates to form a cyst, the surrounding connective tissue and capillaries are stretched and distorted. The capillaries are in close apposition with the duct epithelium, and possibly interdigitate with the epithelium as the cyst forms. Owing to the thickness of the section, the capillaries and epithelium are intermixed in an exaggerated manner (Fig. 5).

In both fibroadenoma and gynecomastia, the capillaries are distributed chiefly around the ducts. There is a profusion of capillaries in fibroadenomas, corresponding to the increased ducts. The distortion of the capillary vasculature in both diseases is closely correlated with the altered outlines of the ducts.

Few intraductal papillomas have been studied. Capillaries with slight branching were demonstrated in the connective-tissue cores of the papillary processes, in contrast with the rare capillaries seen in intraductal hyperplasia.

The alkaline phosphatase method revealed a decreased number of capillaries about the large cysts in fibrocystic disease, in adenosis, and in carcinoma. Since this demonstration of capillaries is dependent on the presence of alkaline phosphatase in the endothelial cells, a decrease of this enzyme would result in a failure to visualize the capillaries. It has been suggested that the

nonspecific alkaline phosphatases consist of a group of enzymes which favor the hydrolysis of esters of monophosphoric acid but differ in effective pH range and in chemical structure.[7] We have performed the alkaline phosphatase reaction at pH 6.4, 7.2, 8.5, 9.1, 9.5, 10.0 and have demonstrated maximum activity at pH 9.5. No increased capillary vasculature was demonstrated around cysts of fibrocystic disease or in adenosis or in carcinoma, at various pH levels.

The significance of decreased capillary size in cases of carcinoma has been demonstrated by the Lepehne-Pickworth peroxidase method. This suggests that there has been an alteration of the normal phosphatase content of the endothelial cells in the area of the tumor. It is pertinent to note that alkaline phosphatase is infrequently demonstrable in breast cancer, in contrast with benign neoplasms of the breast. The diminution of alkaline phosphatase activity is interpreted as a manifestation of altered cellular metabolism. Thin-walled capillaries are in close contact with surrounding tissue fluid and adjacent tissue structures. This may be important in influencing the metabolism of the capillary endothelium.

The significance of decreased capillary vascularity in the large cysts of fibrocystic disease and in adenosis has not been determined. This may be a manifestation of altered alkaline phosphatase metabolism similar to cancer, rather than an actual decreased number of capillaries, or else may be explained more simply on a mechanical basis. The hemoglobin peroxidase technique failed to demonstrate additional vascularity.

The Lepehne-Pickworth peroxidase method has been useful for the demonstration of blood vessels of small size. Since the procedure stains only red blood cells, there is no clear differentiation of the types of blood vessels. Capillaries of variable vascularity may not be uniformly delineated. However, the procedure is a useful adjunct to the alkaline phosphatase technique for the study of capillaries.

Summary

The capillary vasculature of breast tissue can be demonstrated by the histochemical reaction for alkaline phosphatase and peroxidase in thick sections of breast tissue. There is a complex network of capillaries surrounding the ducts and ramifying in the breast lobules. In benign conditions of the breast, the capillaries have a similar distribution, but their arrangement is altered, corresponding to the distortion of the epithelium.

The alkaline phosphatase technique shows a diminished capillary vasculature in the connective tissue surrounding large cysts in fibrocystic disease, in florid adenosis, and in carcinoma. The possibility that the paucity of capillaries demonstrated by this procedure may be due to altered metabolism of capillary endothelial cells is discussed.

Capillaries have been demonstrated in various organs by the alkaline phosphatase technique.

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Failure of Endogenous Serotonin to Produce Lesions of the Carcinoid Syndrome

Studies on Mouse Mastocytoma

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With the Technical Assistance of Margaret Hazel, A.B., and Ruth L. Robertson, H.T. (A.S.C.P.)

The original recognition of the carcinoid syndrome by Isler and Hedinger [1] and its relationship to serotonin, subsequently noted by Thorson and his co-workers,[2] has stimulated much clinical, pharmacological, and morphological interest in this syndrome. It is widely accepted that many of the clinical features of the syndrome are due to serotonin, which is produced by the carcinoid cells. Gosset and Masson, in 1914,[3] were the first to suggest that carcinoids originated from the Kultschitzky cells of the gastrointestinal tract, but it was not until 1952 that Erspamer and Asero [4] demonstrated that the Kultschitzky cell secreted serotonin. Although the morphology of the valvular fibrotic stenosis of the right heart has been described,[3,5-9] the role of serotonin in the production of these lesions has not yet been proved. No valvular lesions were seen by MacDonald [10] and Fiore-Donati and Erspamer [11] following the injection of serotonin into the rat. Davidson and his co-workers [12] administered a serotonin precursor, 5-hydroxytryptophan, into rats, with similar negative results. Steger [13] recently injected 5-oxytryptamine into guinea pigs for varying periods and produced edema of the pulmonary valve, as well as an inflammatory infiltrate of the cardiac muscle; but he did not produce the valvular form of fibrosis usually seen in the carcinoid syndrome. Haverback [14] and MacDonald [15] have produced ulceration of the stomach with large doses of exogenous serotonin.

Recently, Furth [16] and his associates described a transplantable mast-cell tumor in the mouse which produced large quantities of histamine, heparin, and serotonin. Furth reported levels up to 140μg. of serotonin per gram of tumor and up to 714μg. of serotonin per gram of tumor in later transplants.[17] Accordingly, a morphological study was made of the effects of serotonin produced, in vivo, by the mastocytoma in the mouse.

Methods

1. Mast-cell tumor transplants were made in the strain of origin (6- to 8-week-old LAF_1 mice *)

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* Obtained from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

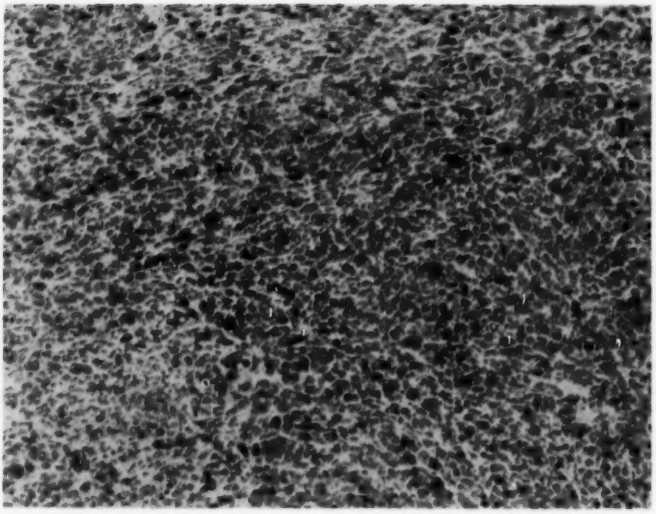

Fig. 1.—Photomicrograph of mast-cell tumor showing sea of rather uniform-appearing cells. Toluidine blue, 0.5%; reduced to 70% of mag. × 200.

by homogenizing in sterile Tyrode's solution tumor tissue removed from the previously killed donor mouse and by injecting approximately 0.5 ml. of the homogenate into the thigh muscle or peritoneal cavity. The mice were then separated into the following groups:

A. Group 1 (12 mice). This group received intramuscular injections of tumor and were placed on an ordinary diet of Purina Laboratory Chow and water ad libitum for a period of three months and were then killed. Periodic determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) were performed according to a modified method of Udenfriend[18] after the sixth week of transplantation.

B. Group 2 (12 mice). Six mice were injected intramuscularly and six were injected intraperitoneally. These mice were not handled after tumor injection, and no urinary determinations of 5-HIAA were made, since the 24-hour fast often resulted in the death of animals. Six survived for a period of nine months and then were killed.

2. Two control groups of 12 mice each were fed Purina Laboratory Chow and water ad libitum and were killed at the end of three and nine months, respectively.

3. Animals were killed individually by ether inhalation and were autopsied immediately. Organs were fixed in 10% neutral formalin. Microscopic examination was made of heart and heart valves,

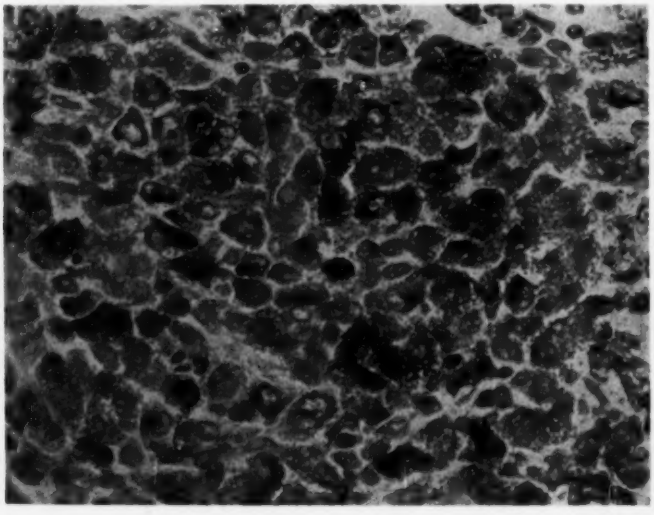

Fig. 2.—Photomicrograph of mast-cell tumor showing heavily granulated tumor cells. Toluidine blue 0.5%; reduced to 70% of mag. × 400.

rolled sections of upper gastrointestinal tract, and kidneys. All sections were stained with hematoxylin and eosin. Sections of heart valves were stained with Verhoeff's elastic tissue stain and Mallory's aniline blue stain. Sections of mast-cell tumor were stained with 0.5% aqueous solution of toluidine blue in order to demonstrate the presence of mast-cell granules.

Results

In the animals receiving tumor injections the daily urinary output of 5-HIAA per mouse ranged from 380μg. to 550μg. Control groups of normal mice excreted from 10μg. to 20μg. of 5-HIAA per day per mouse.

Primary Tumor.—The gross and histologic features of the primary tumor were identical with those described previously by Furth.[16] Grossly, the intramuscular tumor was well preserved, with only small foci of necrosis, and showed a marked tendency to invade surrounding muscle tissue. Animals given intraperitoneal injections showed tumor invasion of the wall of the gastrointestinal tract and distant metastases to the pericardium and pleura. Gross examination failed to reveal metastases to the liver, spleen, kidney, and bone marrow, but in every animal microscopic examination revealed scattered small foci of tumor cells in these organs. Low-power examination revealed the primary tumor to consist of a sea of rather uniform-appearing cells, which were generally small with relatively large nuclei. Under higher power the cytoplasm appeared scant and eosinophilic. No cytoplasmic granules were seen with hematoxylin-eosin stain. There was some variation in size and shape. The nuclei were vesicular with clumped chromatin, and generally round. However, many were irregular and ameboid in shape, resembling reticulum cells. Toluidine blue stain revealed violet cytoplasmic granules in approximately 50% to 70% of the cells. The presence and quantity of the granules varied from area to area and from cell to cell. Occasional mitoses were noted. Areas of necrosis were small and scattered about in large fields of viable tumor.

Heart and Heart Valves.—There was no evidence of subendocardial fibrosis in any of the sections. Occasional fibrous thickening of the valve cusps on both the right and the left side of the heart was noted in all groups of animals, including control groups, and was considered to be a normal finding.

Gastrointestinal Tract.—No ulcerations of the gastrointestinal tract were noted. All sections examined revealed normal mucosal histology.

Kidneys.—No lesions of the kidneys other than the focal interstitial infiltrates of tumor mast cells were noted.

Comment

Page[19] attributed the failure of the repeated administration of exogenous serotonin to reproduce the valvular lesions of the heart in rats to the rapid metabolism of serotonin. That a high level of serotonin production occurred in the present study is clearly indicated by the fact that each mouse excreted daily as much 5-HIAA (380μg.-550μg. per day) as has been reported in many patients with the carcinoid syndrome. However, the plasma levels of biologically active serotonin and the rate of its destruction were not known, since circulating plasma serotonin and monamine oxidase activity of tissue were not measured in this experiment. It has been noted[20-22] that most patients with the full carcinoid syndrome have massive metastases to the liver. Sjoerdsma and associates[23] have shown that serotonin is in part metabolized by liver-cell mitochondria. Massive destruction of the liver may prevent inactivation of serotonin, and thus effect high plasma levels. In this study only microscopic nodules of metastatic tumor were present in the liver, and the liver architecture was essentially intact. Furth[17] suggests that serotonin, as well as other substances, produced by the mast cells are held inactive within the granules of mast cells. However, as previously noted, the metabolic products of serotonin were recovered from the urine in large quantities.

There are a number of other possible explanations for the negative effects of serotonin. First, a species difference must be considered. Second, the duration of the experiment may not have been long enough to produce valvular lesions. In reported cases of the carcinoid syndrome the duration has ranged from 5 months [18] to 21 years.[21] Dunn and Potter [24] have reported a transplantable mast-cell tumor in the DBA strain of mice which kills the animal in 12 to 30 days. They also have searched for the valvular lesions of the carcinoid syndrome, without success.[25] Third, serotonin itself may not be directly responsible for the morphologic lesions of the human syndrome.

Summary

A serotonin-producing mast-cell tumor transplanted in mice was allowed to grow for a period of three to nine months. Despite the production of large quantities for serotonin as measured by urinary 5-HIAA excretions, no morphologic lesions of the heart, heart valves, gastrointestinal tract, or other organs were found.

We wish to express our appreciation to Dr. Jacob J. Furth for providing the donor tumor and some of the animals used in the study. Photographs were made by Mr. Leo Goodman.

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Heterotopic Ossification and Dystrophic Calcification in Infarcted Rat Kidney

A Histochemical Evaluation

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It has been known since the studies of Sacerdotti and Frattin [1] at the turn of the century that ligation of the renal artery and vein with preservation of the ureter is followed by heterotopic ossification of the infarcted renal parenchyma. Their work was followed by a series of descriptive papers on heterotopic ossification in the kidney of the rabbit or dog by Poscharissky (1905),[2] Maximow (1906),[3] Liek (1908),[4] Asami and Dock (1920),[5] and Bridges (1958)[6] and by a single study of this phenomenon in the rat by Bridges (1958).[6] These studies, nevertheless, added only limited information regarding the fundamental mechanisms involved in heterotopic ossification.

Huggins [7] introduced the concept of a tissue inducer when he demonstrated that transplants of epithelium from the urinary bladder would induce bone production within some sites of connective tissue, particularly that in skeletal muscle. On the other hand, epithelium obtained from the stomach, gallbladder, jejunum, or prostate failed to produce such an effect. The stroma of liver and spleen was unresponsive to stimulation. Because of these and ancillary observations, he drew the following conclusions: 1. There appears to be a direct influence of certain specific epithelial cells, such as urothelium,* on connective tissue cells in particular sites to induce bone formation. 2. Only hyperplastic, proliferating urothelium is related to osteogenesis. 3. Connective tissue cells, not epithelial cells, are osteoblastic. 4. Morphologically undifferentiated mesodermal cells (fibroblasts) may and do assume the function of osteoblasts. 5. There is a local increase of alkaline phosphatase at sites of bone production.

Our interest in heterotopic ossification was stimulated by an unusual case of carcinoma of the lung with ossification in metastases to skeletal muscle.[8] In this instance, neoplastic cells containing phosphatase apparently stimulated mesenchymal cells, considered to be fibroblasts within the connective tissue of particular sites, to become functional osteoblasts and form bone. The similarity of this situation to the observations of Huggins was apparent.

Another important consequence of vascular ligation of the kidney is the occurrence of dystrophic calcification of the infarcted parenchyma. The occurrence of dystrophic calcification within infarcted renal parenchyma after occlusion of the renal vasculature was first demonstrated by Litten in 1881.[9] His work was followed by a series of descriptive papers,[10-14] many recently summarized by Edwards,[15] which depicted the principal morphologic features of dystrophic calcification.

We are not aware of any specific study of the role of alkaline phosphatase or of the relationship of acid mucopolysaccharides to calcification within infarcted kidneys. The closest related information must be derived from the studies of various nephropathies

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* The term urothelium is an abbreviation for the transitional epithelium of the urogenital tract. It refers particularly to renal pelvic epithelium in our studies, but generally indicates vesical epithelium in Huggins' studies.

induced experimentally with chemicals. Hepler and Simonds [16] demonstrated calcification in the kidneys of 100% of dogs poisoned with mercury bichloride, of 45% receiving uranyl nitrate, and of 22% following potassium dichromate ingestion. The amount of calcium deposited varied with the agent, the dosage, and the time which elapsed until the death of the animal. Alkaline phosphatase was not associated with the deposition of calcium in the kidneys of these animals. On the contrary, calcification was most prominent in tubular epithelium which had been so severely damaged that this enzyme was inactive or destroyed. They concluded that neither necrosis of cells per se, nor serum calcium levels, nor blood pH, nor alkaline phosphatase was the determining factor for calcification, but related this change to tubular lipid.

Heterotopic ossification and dystrophic calcification observed in the infarcted kidney of the rat appeared to represent a simple and convenient model by which to explore certain histochemical features which might provide pertinent information concerning these processes.

Methods

General Methods.—Thirty-six female Wistar rats, weighing approximately 150 gm., were anesthetized with ether and the left kidney exposed. All of the perirenal tissue was dissected free and the ureter carefully displaced. The renal artery and vein were identified and ligated together with 00 black nonabsorbable surgical (silk) sutures approximately 0.75 cm. from the renal hilus. The wound was closed in layers with black silk. Animals were killed at 2, 3, 5, 7, 14, 21, 27, 33, 40, 47, 60, and 79 days after ligation, either by decapitation or by bleeding from the aorta.

Six additional rats were subjected to ligation of the ureter along with the hilar vessels and killed in pairs at 30, 45, and 60 days. Ten normal rats were also killed at varying intervals to obtain normal blood and tissue as controls.

Biochemical Determinations.—Serum calcium was determined with the Coleman Flame photometer, and serum alkaline phosphatase by the method of Bodansky, on blood samples obtained at the time the animal was killed.

Histologic and Histochemical Methods.—Both kidneys from each animal were quickly removed at the time of death, sliced longitudinally, and fixed, as indicated below. The following techniques were performed as described by Lillie,[17] unless otherwise indicated:

1. Hematoxylin-eosin stain on formalin- and Zenker-acetic acid-fixed tissue.
2. Von Kóssa silver stain for phosphate (calcium phosphate) on formalin-fixed tissue. Tissue fixed in Zenker-acetic acid fluid served as a decalcified control.
3. Thionine 0.5% in M/100 acetate buffer at pH 4 for 30 minutes. Duplicate sections were treated with testicular hyaluronidase (Wydase), 150 TRU per cubic centimeter, with N/10 acetate buffer at pH 5.5 for one hr. at 37 C; with streptococcal hyaluronidase† (20 TRU/mg.), 200 units/cc. in M/10 sodium acetate-acetic acid buffer at pH 5.5 for one hour at 37 C, and with crystalline ribonuclease‡, 1:10,000 in 0.02 M phosphate buffer at pH 6 for one hour at 37 C.
4. Alcian Blue 0.1% in 3% acetic acid at pH 2.6 for 30 minutes before and after enzyme treatments.[8]
5. Rinehart and Abul-Haj's technique [18] before and after enzyme treatments.[8]
6. Periodic acid-Schiff reaction before and after enzyme treatments.[8]
7. Alkaline phosphatase according to the method of Gomori on tissue fixed in 65% alcohol.[19] Duplicate sections were treated with and without substrate to eliminate false localization of enzyme in tissues containing calcium phosphate.
8. Perls' reaction for iron.
9. Oil red O on frozen sections of fresh formalin-fixed tissue.

Results

Serum Calcium and Alkaline Phosphatase.—No significant change in serum calcium or alkaline phosphatase was detected in animals with heterotopic ossification or dystrophic calcification.

General Pattern of Morphologic Change. The most prominent feature in kidneys observed 7 to 21 days after vascular ligation was coagulative necrosis with minimal reparative fibrosis. Nevertheless, within every kidney residual foci of partly viable tissue, predominantly shrunken subcapsular glomeruli, remained. In only a single in-

† Wyeth Laboratories, Inc., Philadelphia.

‡ Nutritional Biochemical Corp., Cleveland.

stance were sparse, minute foci of intratubular calcium present three days after ligation of the major renal vessels. Calcific deposits were present consistently after the seventh day. They appeared initially as fine granular deposits within the necrotic tubular epithelium and were readily appreciated in sections stained by the von Kóssa method, as well as with hematoxylin and eosin. In the latter instance calcium appeared as fine purple, dust-like granules, being first found in necrotic tubular epithelium in the corticomedullary zone and not involving the basement membranes or stromal ground substance. Later it formed extensive band-like zones, involving particularly the inner cortex and outer medulla (Fig. 1). Eventually, large intraluminal concretions were found, and calcium was noted within the interstitium. During later periods calcific aggregates were occasionally surrounded by multinucleated, giant cells of foreign-body type. Iron stains were repeatedly negative. Calcification occurred in all animals in which the vascular and ureteral pedicles were ligated and was unrelated to associated alterations of uroepithelium (*infra vide*).

The renal tubules from the normal contralateral kidney of these rats contained no significant amount of lipid demonstrable by oil red O. Early after infarction most lipid occurred in the medulla near the uroepithelium, with a moderate amount in the subcapsular area. None was observed in those tubules undergoing calcification.

Hyperplasia and proliferation of the urothelium apparently infiltrating the medulla

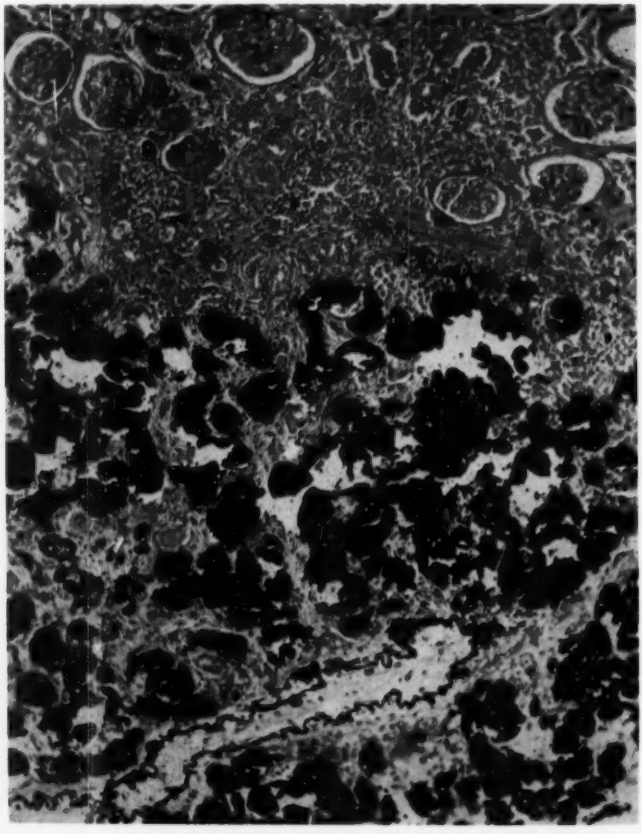


Fig. 1.—Focus of calcification at 40 days. von Kóssa technique; × 125.

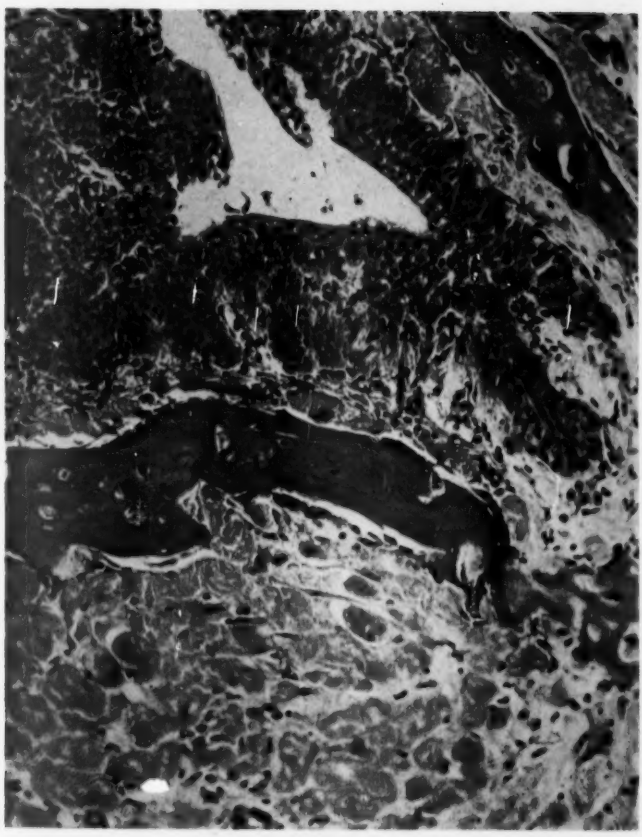


Fig. 2.—Infarcted kidney of rat 27 days after vascular ligation. Bone is evident adjacent to proliferating urothelium. Hematoxylin-eosin stain; ×210.

were prominent by the 27th and 33d days following ligation of the vascular pedicle with preservation of the ureter (Fig. 2). Neither urothelial proliferation nor bone formation occurred in rats whose ureters were ligated along with the hilar vessels. Bone formation began on the 27th day and was noted in all animals with an intact ureter killed after this time. Its close proximity to urothelium was conspicuous. Cartilage formation was not evident in any instance. Osteoblasts were invariably found between urothelium and bone matrix. By 79 days, osteoblastic cells appeared as small, flattened, so-called resting osteoblasts. Cement lines became clearly apparent approximately three weeks after bone formation. Marrow spaces were not observed within the time limit studied. Compensatory hypertrophy of the contralateral kidney became obvious by the 40th day after infarction. Suppuration, principally of the medulla, occurred in four animals but did not inhibit bone production.

Distribution and Apparent Quantity of Alkaline Phosphatase in Elements of Heterotopic Ossification

Day After Ligation	Proliferating Urothelium	Osteoblastic Precursors (Fibroblast-like Cells)	Osteoblasts	Presence of Bone
7	0 to ±	Cells not present	Cells not present	0
14-21	++	++++	Cells not present	0
27-40	0 to ±	Cells not present	++	+

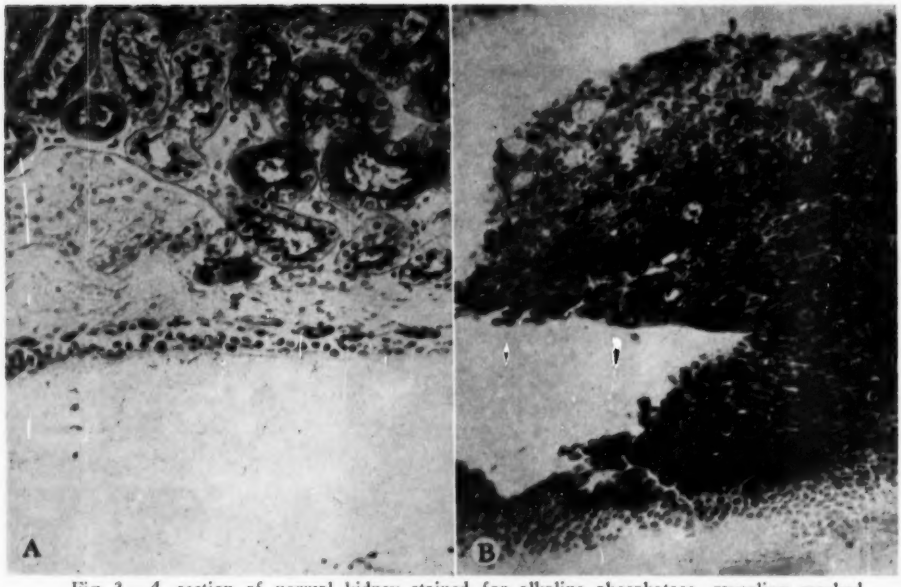


Fig. 3.—*A*, section of normal kidney stained for alkaline phosphatase, revealing marked activity in brush borders of tubules but relatively little in urothelium. Reduced to 72% of mag. × 285.

B, proliferating urothelium with abundant alkaline phosphatase activity 14 days following vascular ligation. Reduced to 72% of mag. × 275.

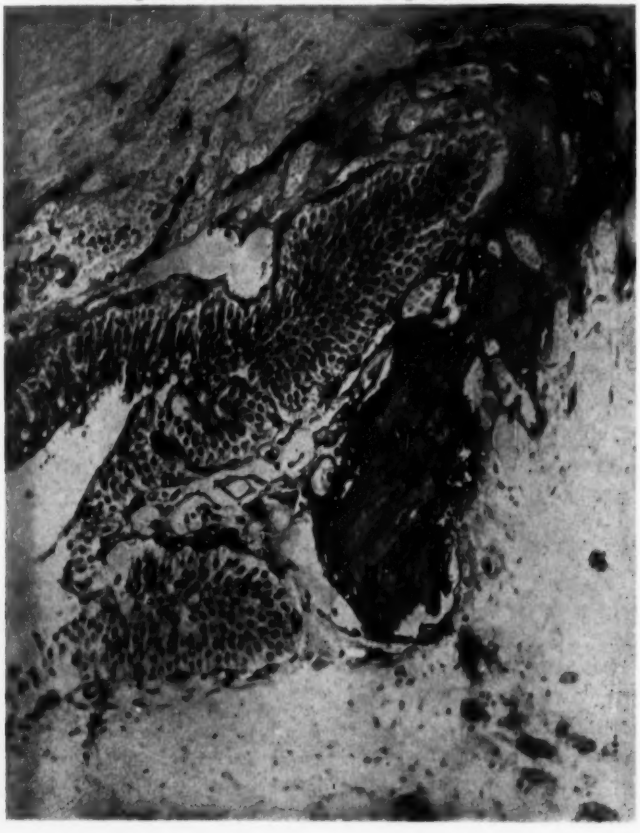


Fig. 4.—Slight alkaline phosphatase activity in urothelium, osteoblasts, and bone 27 days following vascular ligation. × 195.

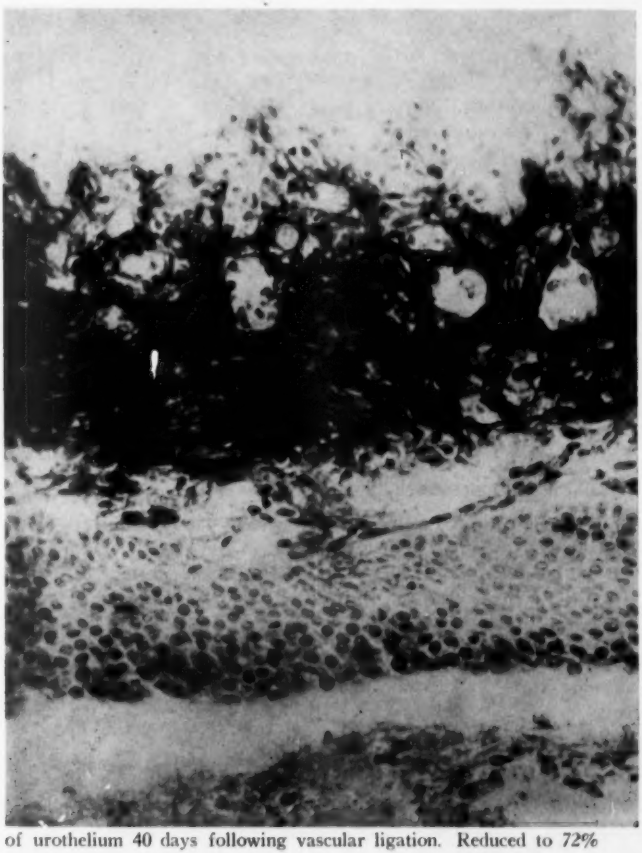
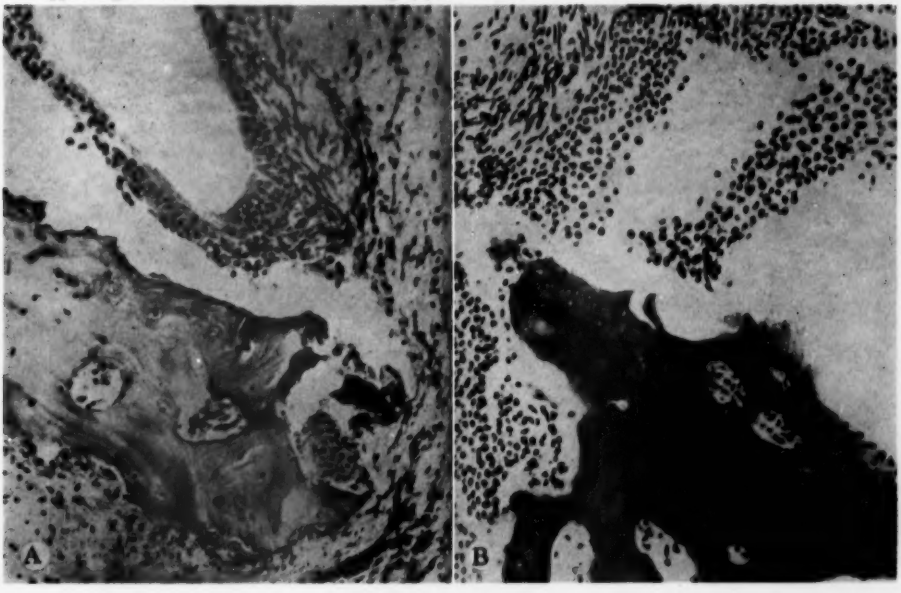


Fig. 5.—Abundant alkaline phosphatase activity in precursor site of new-bone formation 14 days following vascular ligation. × 285.

Fig. 6.—*A*, basophilia of urothelium 40 days following vascular ligation. Reduced to 72% of mag. of × 235.

B, abolition of basophilia after ribonuclease digestion, but bone is more metachromatic, appearing black. Reduced to 72% of mag. × 275.



Alkaline Phosphatase.—This enzyme was notably absent at sites of dystrophic calcification. The distribution and apparent quantity of alkaline phosphatase in relation to heterotopic ossification are summarized in the accompanying Table. Ligation of the renal vasculature resulted in depletion of alkaline phosphatase in the tubules of the infarcted kidney. On the other hand, proliferating urothelium contained cytoplasmic alkaline phosphatase, which appeared most abundant (2+) at the 14th and 21st days following ligation (Fig. 3*A* and *B*) and declined by the time bone was formed (+ to ±; Fig. 4). Most intense staining reactions for alkaline phosphatase (4+) were found in osteoblastic precursors (cells having the morphologic appearance of fibroblasts) between the 14th and the 21st day (Fig. 5). These cells were always found in close association with urothelium but appeared to be derived from the connective tissue of the renal stroma. By the time bone was formed, osteoblasts contained cytoplasmic phosphatase in lower concentrations (2+), and late, resting osteoblasts contained even less. The peripheral rim of newly formed bone also contained phosphatase, as did young osteocytes.

Ribonucleoprotein and Acid Mucopolysaccharide.—Urothelium, proliferating urothelium, and osteoblasts all manifested cytoplasmic metachromasia, abolished by ribonuclease but not by testicular hyaluronidase, indicating that this tinctorial reaction in such cells was due to their ribonucleic acid content rather than to acid mucopolysaccharide. The variable metachromasia of

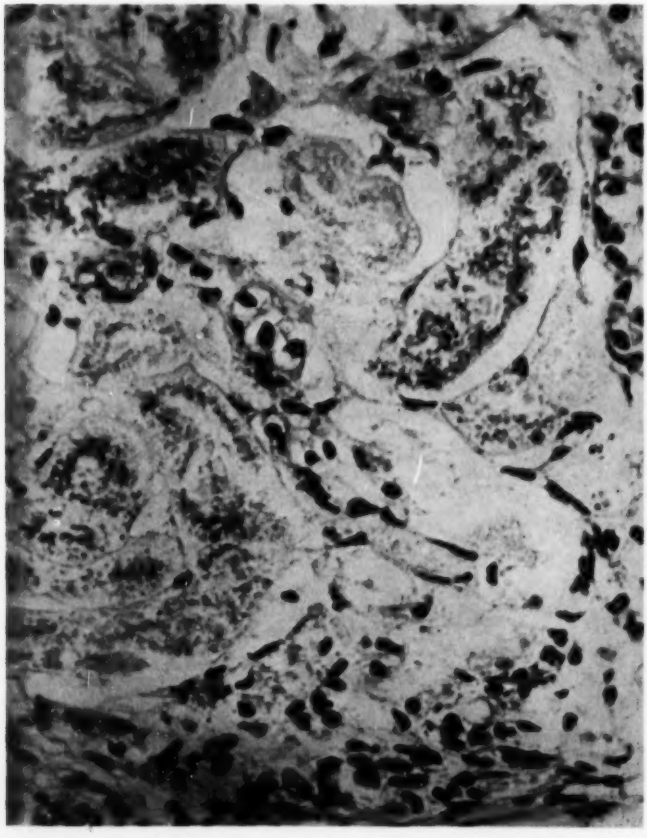


Fig. 7.—Metachromatic intracellular droplets at 21 days, corresponding to sites of early calcific foci. Thionine; × 500.

bone matrix was unaffected by hyaluronidase and became more intense after ribonuclease pretreatment (Fig. 6*A* and *B*).

Bone matrix and the cytoplasm of osteoblasts were also colored by the Alcian Blue, Rinehart and Abul-Haj, and periodic acid-Schiff techniques. These reactions were not inhibited by prior hyaluronidase or ribonuclease digestion. On the other hand, metachromasia and positive Rinehart and Abul-Haj and Alcian Blue reactions of renal ground substance were inhibited by prior treatment with testicular and streptococcal hyaluronidase. However, the positive periodic acid-Schiff reaction at this site was unaffected by the enzymatic treatments.

Metachromasia and positive Alcian Blue and Rinehart and Abul-Haj reactions were observed simultaneously with the appearance of calcium in tubules undergoing dystrophic calcification. These reactions were unaffected by hyaluronidase pretreatment (Figs. 7 and 8).

Phosphate (Calcium Phosphate).—Positive von Kóssa reactions were first observed at seven days in renal tubules undergoing dystrophic calcification. Phosphate (calcium phosphate) appeared in bone matrix and well-formed bone when such structures were recognized. No reactive sites were evident in the stromal sites of future bone formation. Iron stains were consistently negative at the sites of positive von Kóssa reactions.

Comment

The results confirm previous investigations indicating that proliferating urotheli-

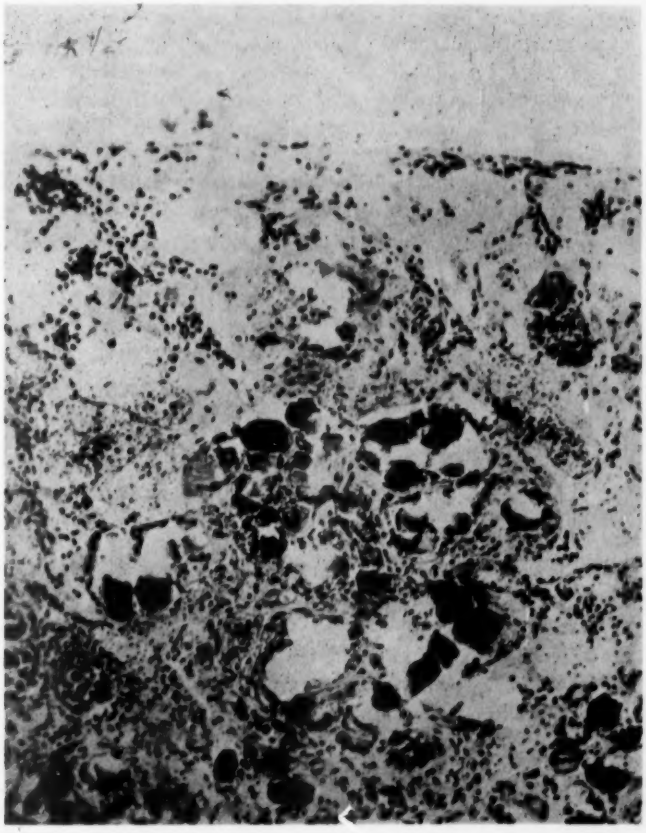


Fig. 8.—Rinehart-Abul-Haj-positive focus at 79 days, corresponding to site of calcification. × 150.

um is associated with heterotopic ossification within infarcted renal medullary stroma. That these changes are largely dependent upon local phenomena is apparent from the normal blood calcium and alkaline phosphatase values observed.

The fact that heterotopic bone is found only in close association with hyperplastic urothelium strongly suggests that the urothelium must play some significant role in its induction. It is noted that these cells possess abundant alkaline phosphatase activity, which reaches a maximum prior to ossification, and an apparently high concentration of ribonucleic acid, as evidenced by their basophilia, which is labile to ribonuclease. It is significant that a similar cytochemical profile is observed in cells morphologically and functionally interpreted as osteoblasts and their precursor forms. It has been suggested that the combination of alkaline phosphatase and ribonucleoprotein in such cells is related to the elaboration of scleroproteins in osseous, as well as nonosseous, sites.[20] Since scleroprotein represents a major constituent of bone matrix, it would appear that alkaline phosphatase is concerned with the formation, rather than the calcification, of bone matrix. This interpretation is consistent with the views of Pritchard concerning the role of alkaline phosphatase in bone formation.[20,21] Indeed, the occurrence of calcification in the absence of alkaline phosphatase further tends to support this contention.[22,23] The precise role of proliferating urothelium in this scheme of events is difficult to establish. Why or how it stimulates the mesenchymal cells of infarcted renal parenchyma to assume an osteoblastic role still remains enigmatic. Suffice it to note that proliferating urothelial cells possess cytochemical features similar to those observed in fibroblastic precursors and osteoblasts. A decline in staining intensity in the former is accompanied by an increase in the latter, and bone formation was not observed without this sequence.

The findings recounted above are morphologically and cytochemically similar to those observed in normal membranous-bone formation.[20] In addition, the situation is analogous to that observed in metastatic tumors exhibiting ossification.[6]

The significance of acid mucopolysaccharide in bone formation has been recounted by Snapper,[23] who has noted that such material is present in all tissue in which calcium is deposited. He has suggested that these mucopolysaccharides may act as a cation exchange resin capable of concentrating calcium. We have not explored the mechanisms of calcification of bone matrix in this study but can confirm the existence of such a relationship at the sites of dystrophic calcification within the kidney. The findings in this study do, however, suggest that the acid mucopolysaccharide of bone matrix is derived from osteoblasts rather than the renal ground substance. The latter tinctorially exhibits the features of acid mucopolysaccharides of the hyaluronic acid type, exhibiting lability to both testicular and streptococcal hyaluronidase,[24] whereas that evident in osteoblasts and bone matrix is resistant to such enzymatic treatments.

This study clearly demonstrates an association between calcium deposits and acid mucopolysaccharides and indicates their simultaneous appearance in cells undergoing dystrophic calcification. The relationship between calcification and acid mucopolysaccharide has received considerable attention.[22,23,25,26] According to Snapper and Gechman,[23] chondroitinsulfuric acid must play an important role in calcification because all tissues in which calcium is deposited contain this mucopolysaccharide. We have confirmed this observation in arteriosclerotic plaques, tuberculous lesions, and the calcified mitral annulus.[27] The identification of the acid mucopolysaccharide observed in calcification in this study as chondroitinsulfate utilizing hyaluronidase pretreatment is not wholly consistent with the effects of this enzyme on this mucopolysaccharide in vitro, as described by Meyer.[28,29] Nevertheless, the findings do

parallel the results expected with this type of mucopolysaccharide in tissue sections.[30] Snapper notes that chondroitinsulfuric acid may act as a cation exchange resin capable of concentrating calcium. It is unlikely that either the calcium or the mucopolysaccharide is derived exclusively from the particular parenchymal cell in which it is first found. Since the amounts of calcium and acid mucopolysaccharide undergo marked local increases, it appears probable that they are derived from the circulation, possibly from the anastomoses which develop between the capsular surface and adjacent tissue, rather than from preexistent trapped serum.

The state of the renal circulation has been said to play a role in dystrophic calcification. Litten, in 1881, originally claimed that total occlusion of the renal circulation was not followed by calcification.[9] He hypothesized that parenchymal damage and partial reestablishment of the renal circulation were both essential for calcification. However, Pugh, in 1927, did produce extensive calcification by total ligation of the renal artery.[11] More recently, Edwards [16] could not produce calcification after total ligation in dogs studied at 14 days. In this study in the rat, it is evident that total ligation of the renal artery and vein, as well as ureteral vessels, results in renal infarction, which is accompanied by dystrophic calcification. It is to be noted, however, as indicated above, that vascular anastomoses between the renal capsule and surrounding tissue may play a significant role in this process.

The results of this study and those concerned with dystrophic calcification following the administration of some chemical nephrotoxins are mutually corroborative. Both reveal that dystrophic calcification occurs independently of changes in serum calcium or serum alkaline phosphatases at sites where tissue alkaline phosphatase is absent or markedly depleted. It is apparent that such enzymatic activity is unrelated to dystrophic calcification, whereas observations of heterotopic ossification in the same kidneys demonstrate an important role for this enzyme in bone formation rather than its calcification. This is additional evidence that a surcharge of calcium by itself does not predispose to bone formation. In contrast with the results of the study of Hepler and Simonds,[16] we have found no relationship between lipid deposits and calcification. The former were not evident at sites prone to calcification.

Summary

Heterotopic ossification was consistently observed in the infarcted kidneys of rats 27 days after ligation of the renal vessels only when the ureter was left intact. Dystrophic calcification was first noted at seven days and appeared despite ureteral ligation. The former process was invariably preceded by hyperplasia of pelvic urothelium. These cells contain abundant ribonucleic acid and alkaline phosphatase activity, which diminishes at the time a transition of stromal fibroblasts to osteoblasts (fibrocytes with abundant alkaline phosphatase and ribonucleoprotein content) occurs. The significance of this reciprocal relationship in regard to the mechanism whereby stromal cells are stimulated to osteoblastic activity is inapparent.

Sequential studies of the process of heterotopic ossification indicate that alkaline phosphatase activity is more directly concerned with the formation of bone matrix than with its calcification, and that the acid mucopolysaccharide observed in bone matrix appears to be derived from osteoblasts rather than the renal ground substance. The absence of alkaline phosphatase at sites of dystrophic calcification signifies that this enzyme is of little importance in this process.

The possibility that acid mucopolysaccharide, histochemically of the chondroitinsulfate type, may serve as a cationic exchange resin capable of concentrating calcium is suggested by the similar temporal relationship exhibited by these substances in dystrophic calcification.

The findings reveal a similarity in heterotopic ossification within the infarcted kidney, membranous-bone formation, and the ossification noted in some metastatic neoplasms.

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Intracranial Involvement from Carcinoma of the Lung

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In a pilot study of 100 consecutive cases of carcinoma of the lung, in 92 of which the brain was included in the postmortem examination, intracranial metastasis occurred in 30, that is, in a ratio of 1 in 3.[1] Involvement of the brain was exceeded in frequency only by metastasis to lymph nodes, liver, and adrenal glands. The brain was involved more frequently than was the skeleton, the pancreas, or the kidneys. Furthermore, the frequency of intracranial involvement bore no relationship to the cell type. The present study was undertaken to ascertain the validity of these observations in a larger number of consecutive cases examined under similar conditions and to record any additional pertinent information.

The necropsy records of the Veterans Administration Hospital, Houston, Texas, were surveyed for the period Oct. 1, 1949, through Sept. 11, 1958. During this time, 3,000 necropsies were performed on male patients, comprising almost 90% of the patients who died in the hospital. Of those examined, 2,204 were white and 796 were Negro. Carcinoma of the lung was observed in 363 of the patients, 297 white and 66 Negroes. The preserved lungs and the brains, when involved, as well as photographs of most of them, were available for study. Microscopic preparations from the primary site and from all locations listed in the anatomic diagnosis were reviewed.

Clinical Observations

Frequency.—The ages of all the patients examined after death and of those with carcinoma of the lung are given in Table 1.

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The frequency of carcinoma of the lung among the 3,000 patients examined was slightly over 12%. The youngest patient with carcinoma of the lung was 23 and the oldest 81 years of age. Carcinoma of the lung was most frequent among patients in the sixth decade of life. Of the 3,000 patients examined, 2,065 died after age 50, and 284 of these had carcinoma of the lung, comprising 78% of all patients with carcinoma of the lung.

Of the 363 patients with carcinoma of the lung, the brain was examined in 338. Among these, intracranial involvement was recorded in 129 instances, comprising 38.1% of the brains examined. Of these patients, 4 were in the third decade, 12 (2 Negro) in the fourth, 25 (9 Negro) in the fifth, 46 (10 Negro) in the sixth, 39 (8 Negro) in the seventh, and 3 in the eighth decade of life.

As shown in Table 2, among 75 patients 50 years of age or younger, involvement of the brain occurred in 41 (54.6%). Among the 263 patients over 50, involvement of the brain was observed in 88 (33.4%). Accordingly, carcinoma of the lung involved

TABLE 1.—*Carcinoma of Lung Among 3,000 Patients Examined After Death*

	All Patients			Patients with Carcinoma		
Age, Yr.	Total	W	N	Total	W	N
Unknown	4	1	3	--	--	--
Under 30	182	141	41	6	6	--
31-40	371	259	112	21	16	5
41-50	378	282	96	52	41	11
51-60	843	636	207	141	120	21
61-70	1,031	705	326	123	96	27
71-80	162	152	10	19	17	2
81 & over	29	28	1	1	1	--
Total	3,000	2,204	796	363	297	66

TABLE 2.—*Intracranial Involvement from Carcinoma of Lung*

Age	Carcinoma of Lung	Brains Examined	Intracranial Metastasis	Per Cent
21-30	6	5	4	
31-40	21	21	12	54.6
41-50	52	49	25	
51-60	141	133	46	
61-70	123	112	39	33.4
71-80	19	18	3	
81 & over	1	0	0	
Total	363	338	129	

TABLE 3.—*What Cell Type Is More Likely to Metastasize to the Brain?*

	Metastases to Brain		No. of Cases	Per Cent
Squamous-cell	63	of	178	35.4
Reserve-cell	32	of	79	40.5
Columnar-cell	18	of	37	48.6
Mixed-cell	16	of	44	36.4
Total	129	of	338	38.1

the brain more frequently before the age of 50 and significantly less often after 50.

Cellular Structure.—Among the 363 carcinomas of the lung, 189 were squamous-cell (52%); 88 were reserve-cell (24%); 40 were columnar-cell (11%), and 45 were mixed-cell carcinoma (12%)—squamous- and columnar-cell, 38; squamous- and reserve-cell, 5; squamous-, columnar-, and reserve-cell, 2. In one instance the neoplasm was a malignant argentaffin-cell tumor.

The cell types of intracranial metastases are given in Table 3. These data suggest that the frequency of intracranial involvement bears no significant relationship to the cell type. However, columnar-cell carcinomas metastasizing to the brain were relatively high, and of the carcinomas involving the hypophysis, 14 of the 26 were the reserve-cell type.

Spread.—Local extension and involvement of lymph nodes occurred in 310 of the 363 patients (85.3%). Metastatic foci were encountered in the liver 161 times (44.3%), in the adrenal glands 139 times (38.3%), in the opposite lung 102 times (28.1%), in the pleura, diaphragm, and chest wall 87 times (24%), in the skeleton 79 times (21.7%), in the heart, including the pericardium, 77 times (21.2%), in the kidneys 74 times (20.3%), in the pancreas 54 times (14.8%), and in the spleen 31 times (8.5%). The frequency of intracranial involvement, 38.1%, from carcinoma of the lung was exceeded in frequency only by involvement of lymph nodes, liver, and adrenal glands. As shown in Table 4, different organs seemed to be favored for metastasis by various cell types. Among the 161 instances of metastasis to the liver, 65

TABLE 4.—*Distribution of Metastases from Carcinoma of the Lung*

Site	Squamous-Cell	Reserve-Cell	Columnar-Cell	Mixed-Cell	Argentaffin-Cell	Total	Per Cent
1. Lymph nodes	151	86	35	37	1	310	85.3
2. Liver	65	56	21	18	1	161	44.3
3. Adrenal glands	54	47	19	19		139	38.3
4. Brain	63	32	18	16		129	38.1
5. Opposite lung	47	20	20	15		102	28.1
6. Pleura, diaphragm, chest wall	50	15	13	9		87	24.0
7. Skeleton	36	17	12	14		79	21.7
8. Heart and pericardium	40	17	12	8		77	21.2
9. Kidneys	37	17	8	12		74	20.3
10. Pancreas	11	34	4	4	1	54	14.8
11. Spleen	9	13	2	6	1	31	8.5
12. G.I. tract	19	8	2	2		31	8.5
13. Peritoneum	11	5	6	4		26	7.1
14. Skin	8	8	1	1		18	5.0
15. Gallbladder	3	6	1	1		11	
16. Spinal dura or cord	4	2		1		7	
17. Prostate	1	4		1		6	
18. Urinary bladder		1		1		2	

were squamous-cell and 56 were reserve-cell carcinoma. Of the 139 instances of metastasis to the adrenal glands, 54 were squamous-cell and 47 reserve-cell. In the pancreas metastasis was recorded in 54 instances, with 34 reserve-cell and 11 squamous-cell. In the spleen there were metastases in 31 instances, of which 13 were reserve-cell and 9 were squamous-cell.

Site.—The main growth was located in the right lung in 193 patients and in the left lung in 158 patients. Of the remaining 12 patients, the exact site could not be determined in 10, was considered to be bilateral in 1, and originated in the trachea in 1. Among the 129 patients with intracranial involvement, the metastasis in the brain was solitary in 44 and occurred in multiple foci in 85. Solitary foci were located in the cerebral hemispheres 17 times (9 in the left and 8 in the right), in the cerebellar hemispheres 6 times (5 in the left and 1 in the right), and once each in the midbrain and the pons. The dura mater was the only site of involvement in five instances. Involvement of the hypophysis was encountered 26 times, in 13 of which it was the only site of intracranial involvement. Metastasis to the pineal body was recorded three times, being once the only site of intracranial involvement. Multiple foci were encountered in the cerebral hemispheres 71 times, in the cerebellar hemispheres 28 times, in the dura mater 23 times, in the medulla oblongata 6 times, in the pons 5 times, in the glomus choroideum twice, and in the leptomeninx once.

Methods of Diagnosis.—Of the 363 patients who died with carcinoma of the lung, the clinical diagnosis of carcinoma of the lung was not made at all or was not made with certainty in 70. Diagnosis was made by roentgenographic study alone in 42 patients. Exploratory thoracotomy confirmed the clinical diagnosis in 45 patients, pneumonectomy in 31, lobectomy in 12, and craniotomy in 7. Of the remaining 156 patients, the diagnosis was established during life by bronchoscopic biopsy in 50, by examination of bronchial washing alone in 7, by lymph node biopsy in 50, by skeletal biopsy in 14, by skin and muscle biopsy in 11, by needle biopsy of the liver in 8 and of the lung in 4, by examination of thoracentesis fluid in 6, by laparotomy in 4, and by examination of coughed-up sputum in 2. According to these data, no surgical approach had been made in nearly one-third of the patients examined.

Clinical Manifestations.—Among the 129 patients with intracranial metastasis, 30 had clinical signs and symptoms of intracranial involvement as the presenting complaint. In 51 additional patients clinical manifestations of central nervous system involvement were recognized in the course of their illness. The condition of most of the remaining 48 patients went "rapidly downhill," and they died with no localizing symptoms recorded.

Duration.—The time lapse between the appearance of any symptoms of carcinoma of the lung and the death of the 363 patients was one year or less in 309, or 85%. In the remaining patients the duration of illness was unknown in 8 patients, was between one and two years in 32, between two and five years in 13, and over five years in 1 patient. Among the 14 patients who survived longer than two years, the carcinoma was squamous-cell in 7, reserve-cell in 4, columnar-cell in 2, and mixed squamous- and columnar-cell in 1.

Report of Cases

The following reports illustrate the clinical manifestations, duration of illness, and central nervous system involvement.

CASE 1.—A 39-year-old white man was admitted Nov. 4, 1957, because of paralysis of the left arm for two weeks. The patient had been in good health until five weeks before admission, when he fell and struck the back of his head. After this, he developed some swelling of the lower back and a severe headache over the right eye. Two weeks prior to admission the left side of the face became paralyzed, and he could not move the left arm. The paralysis subsided somewhat, but the headache persisted. One week prior to admission he lost consciousness while at work and entered another hospital. At this time a spinal fluid examination revealed 790 erythrocytes per cubic millimeter with

a total protein of 116 mg. per 100 cc. A bronchoscopic biopsy was reported as negative. He then was transferred to this hospital.

At the time of admission, he appeared dehydrated and disoriented, responding only to painful stimuli. The temperature was 99.2 F; pulse rate 76, and blood pressure 138 mm. Hg systolic and 90 mm. diastolic. Neurologic examination disclosed a left central facial palsy and left upper-extremity paralysis.

Urinalysis revealed a trace of albumin, 6 to 8 white blood cells per high-power field, and 1 coarsely granular cast per low-power field. The hematocrit was 44%, with the hemoglobin content 15 gm. per 100 cc. The white blood cell count was 14,450 per cubic millimeter, with the differential count normal. The VDRL test of the blood was negative. Roentgenographic examination of the chest revealed a homogeneous soft-tissue mass in the left upper lung field and hydrothorax. On Nov. 6, carotid arteriography revealed changes compatible with multiple cerebral lesions. His condition deteriorated rapidly, and he died on Nov. 8, 1957.

Pathological Findings.—At necropsy (12 hours after death), the left lung was seen to be partly collapsed and weighed 600 gm. At the apex was a circumscribed mass of friable neoplastic tissue 5 cm. in diameter (Fig. 1). The right lung weighed 800 gm. and appeared uninvolved. Some of the hilar lymph nodes were partly replaced by neoplastic tissue, as were the left adrenal gland, pancreas, and kidneys. The brain weighed 1,450 gm. The cerebral hemispheres appeared asymmetrical. There were dark red-brown areas of hemorrhage beneath the dura over the frontal and temporal regions. The cerebral hemispheres were dotted with gray-black, circumscribed nodules. Brain substance was destroyed over the orbital surface of the right frontal lobe, in an area 5×4 cm., and 2 cm. deep, with the space lined with ragged tissue debris. On the right, a tentorial pressure groove, with herniation up to 1 cm., extended the whole length of the hippocampal gyrus. On the left, the occipital pole protruded and extended 2 cm. farther than on the right, and the brain substance was thinned by a mass immediately underlying the thin layer of cortical tissue. The topographic relation of the midline structures was distorted. On transverse cut surfaces of the midbrain just anterior to the pons the left side was observed to be softened. Horizontal cut surfaces of the cerebellar hemispheres and pons revealed extravasation of blood into the cistern over the basilar artery. On coronal cut surfaces of the cerebral hemispheres at the level of the optic chiasm the two sides were asymmetrical, with the right larger than the left and the median structures pushed from right to left. Coronal cut surfaces 4 cm. anteriorly

Figs. 1 to 3.—Carcinoma of the lung in a white man, aged 39.

Fig. 1.—The primary site is in the upper lobe of the left lung.

and at the level of the temporal poles revealed massive extravasation of blood with destruction of the brain substance over an area 5×3 cm. on the right and 3×1.8 cm. on the left (Fig. 2). On cut surfaces 3 cm. posteriorly the brain substance was discolored and destroyed over the convex surface of the hemisphere, 3×3 cm., on the right. There were several nodular areas of similar destruction from 0.5 to 1 cm. immediately beneath the cortical tissue, leaving a rim of about 0.3 cm. uninvolved. On further cut surfaces 3 cm. posteriorly there was a central area of destruction of the brain substance 2 cm. in diameter, not reaching the cavity of the lateral ventricle.

Microscopic structure of the neoplastic tissue in the brain was that of squamous-cell carcinoma (Fig. 3). Pertinent findings in the anatomic diagnosis were carcinoma, squamous-cell, of lung, left, with metastasis to regional lymph nodes, left adrenal gland, pancreas, kidneys, and brain with hemorrhage, massive.

Case 2.—A 46-year-old white man was admitted to another hospital on March 2, 1958, because of severe headache of two weeks' duration and blurred vision. The headache commenced shortly after he had been in a minor automobile accident in which

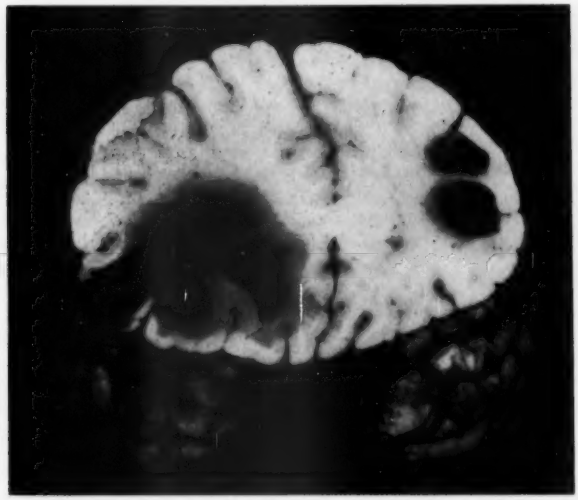


Fig. 2.—The brain is extensively involved. The convolutions are flattened; the brain substance is distorted, and there is massive hemorrhage.

he hit his head against the windshield and steering wheel. He did not lose consciousness at any time and was alert and oriented immediately after the accident. However, several days later, the headache spread over his entire head. Later, he noted that, while driving, his vision was blurred and he could not distinguish clearly the automobile in front of him. At that time the patient became drowsy and slept almost continuously for three days. One day prior to admission, he became nauseated and mentally confused. At the time of admission he appeared well developed, though poorly nourished. His speech was normal, and he appeared oriented as to time, person, and events. Neurologic examination revealed some diminution of vision of the left eye. The pupils were pinpoint, round, and regular. Ophthalmoscopic examination could not be performed. Light reflex was sluggish. Corneal reflex was present bilaterally. There was a questionable Babinski sign bilaterally, but it was more definite on the right. Pinprick and light touch perceptions were normal in both upper and lower extremities. Stereognosis and position sense were normal. A ventriculogram and a right carotid arteriogram revealed a space-occupying lesion in the posterior portion of the right cerebrum. On March 4, a craniotomy was performed, and a large neoplasm in the right occipital lobe was removed. The microscopic structure of the neoplasm was columnar-cell carcinoma. On

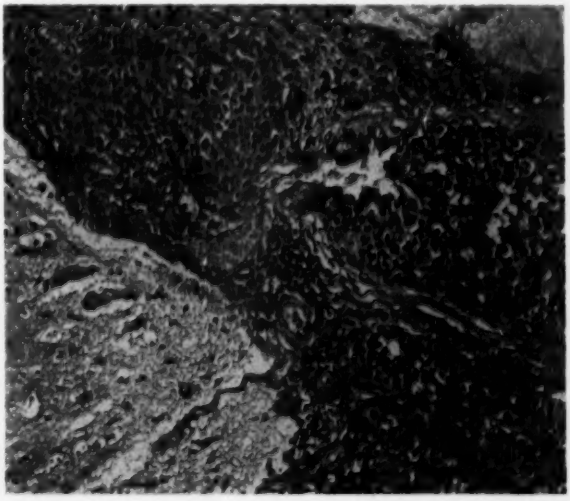


Fig. 3.—The microscopic structure is squamous-cell carcinoma, as shown in the cerebral metastasis. × 100.

March 10, 1958, roentgenographic examination of the chest revealed numerous destructive areas in the posterior portion of the right fifth rib. There were a slightly increased density in the lung parenchyma underlying these lesions and a linear area of increased density, probably atelectasis, in the right lower lung field.

On March 19, the patient was transferred to the Veterans Administration Hospital, Houston, Texas. At the time of admission he appeared markedly emaciated, alert, and oriented. The craniotomy scar was well healed. The temperature was 98.6 F; pulse rate 125, and blood pressure 120 mm. Hg systolic and 86 mm. diastolic.

Urinalysis gave essentially negative results; the hematocrit was 41%; the hemoglobin content 12.8 gm. %. The white blood cell count was 11,950, with a normal differential count. The Kahn test of the blood was negative.

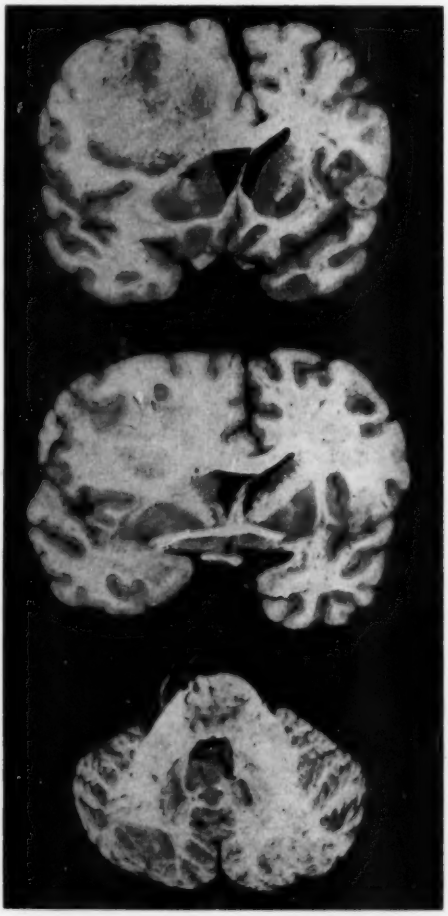
On April 8, deep x-ray therapy to the head was commenced and 3,000 r was delivered in two weeks. The patient's physical condition remained relatively stable for two months. On June 22 he suddenly had a generalized seizure, lasting three minutes. Following this, his condition improved, and he was discharged from the hospital on June 30. On July 27, he returned in a terminal state. Neurologic examination revealed left hemiparesis with bilateral ankle clonus and bilateral Babinski sign. An emergency tracheostomy was performed. Epileptiform seizures recurred with increased frequency. He became comatose and died on Aug. 14, 1958.

Figs. 4 to 6.—Carcinoma of the lung in a white man, aged 47.

Fig. 4.—The growth was primary in the right lower-lobe bronchus.

Pathological Findings.—At necropsy (two hours after death), the right lung weighed 520 gm., and a firm neoplastic mass, 4 cm. in diameter, was observed in the right lower lobe near the mediastinal surface (Fig. 4). Neoplastic tissue also replaced many of the regional and retroperitoneal lymph nodes and involved the left adrenal gland, the liver, the left kidney, and the skeleton. The brain weighed 1,390 gm. In the occipital lobe of the right cerebral hemisphere was an area of yellow necrotic involvement, 4 cm. in diameter. In the right frontal lobe was an area of similar involvement 1 cm. in diameter. About the olfactory bulb on the right was another area of neoplastic involvement, 2 cm. in diameter. On coronal cut

Fig. 5.—As revealed in a right frontoparietal craniotomy, neoplastic mass occupies much of the right cerebral hemisphere, causing distortion of the ventricles. There is also a metastatic nodule in the left cerebellar hemisphere.



surfaces of the cerebral hemispheres at the level of the optic chiasm were four nodules of neoplastic involvement, 0.5 to 2 cm. in diameter, in the centrum semiovale. On parallel cut surfaces just behind the anterior poles of the temporal lobes a neoplastic area 4.5×4 cm., involved the right cerebral hemisphere, extending to the surface and reaching the corpus callosum. Two smaller nodules were below this. The median line was pushed from right to left, with marked herniation under the falx cerebri. On further cut surfaces posteriorly, multiple small neoplastic nodules appeared. On cut surfaces 5 cm. anterior to the occipital poles both lobes were seen to contain neoplastic nodules, more especially in the right. Horizontal cut surfaces of the cerebellar hemispheres showed neoplastic involvement in the left, 3×2.5 cm., extending in places to the cortex. A small neoplastic nodule was also present in the right dentate nucleus (Fig. 5).

The microscopic structure of the neoplasm was that of columnar-cell carcinoma (Fig. 6). Pertinent findings in the anatomic diagnosis were scars of operation: craniotomy, right frontoparietal, for carcinoma, metastatic, of cerebral hemisphere, occipital region; tracheostomy; carcinoma of lung, columnar-cell, right lower lobe, with metastasis to regional and retroperitoneal lymph nodes, cerebral and cerebellar hemispheres, left adrenal gland, liver, left kidney, and skeleton; emphysema of lungs; chronic passive hyperemia of viscera; thrombi, organizing, in periprostatic vessels; infarct of lung, right middle lobe; pneumonia, organizing; emaciation.

CASE 3.—A 59-year-old Negro man was admitted Aug. 26, 1955, because of chest pain and persistent cough for three weeks. At the time of admission he appeared well nourished; the temperature was 98.8 F; pulse rate 72, and blood pressure 140 mm. Hg systolic and 80 mm. diastolic.

Urinalysis and blood cell counts were essentially normal. The VDRL test of the blood was negative. Roentgenographic examination of the chest revealed a coin lesion 2 cm. in diameter in the right lower lobe. On Aug. 31 a right lower lobectomy was performed. In the center of the resected lobe was a circumscribed nodule of neoplastic tissue, 2×1.5 × 1 cm. The microscopic structure of the neoplasm was reserve-cell carcinoma. Following recovery from the operation, the patient remained asymptomatic until May, 1957, when roentgenographic studies suggested recurrence of the neoplasm. Bronchoscopic biopsy and bronchial washings at this time revealed recurrent reserve-cell carcinoma. He then received a course of radiation therapy on the 2 MEV machine.

On Feb. 3, 1958, he was readmitted to the hospital because of speech difficulty and urinary incontinence for two and one-half weeks. At the time of this admission he still appeared well nourished. The temperature was 98 F; pulse rate 90, and blood pressure 135 mm. Hg systolic and 80 mm. diastolic.

Urinalysis revealed a trace of albumin and 15 to 18 white blood cells per high-power field. The white blood cell count was 5,600. The hemoglobin content of the blood was 14.6 gm. %. Roentgenographic examination of the chest was reported as

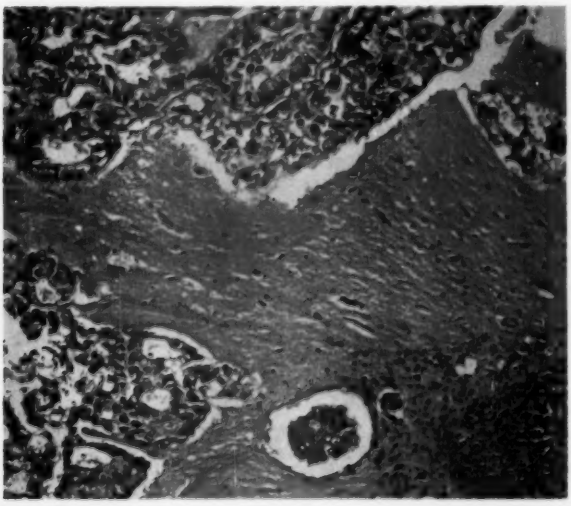
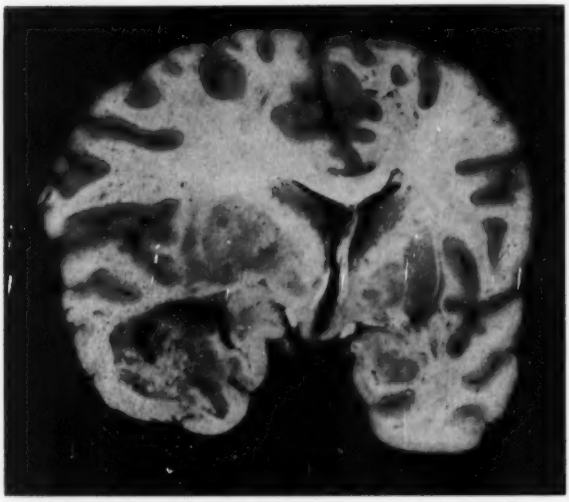


Fig. 6.—The microscopic structure is columnar-cell carcinoma, as shown in the cerebellar metastasis. × 100.



Figs. 7 and 8.—Carcinoma of the lung in a Negro man, aged 62. Lobectomy of the right lower lobe for "coin lesion" in 1955 revealed reserve-cell carcinoma.

Fig. 7.—He died of intracranial metastasis in 1958.

essentially negative. A bilateral carotid arteriogram suggested a space-occupying lesion in the right frontal lobe. The patient's condition rapidly deteriorated, and he died Feb. 14.

Pathological Findings.—At necropsy (five hours after death) the remaining upper and middle lobes of the right lung weighed 300 gm. The lumen of a large branch of the pulmonary artery was occluded by a thrombus. Neoplastic tissue was not recognized. No pertinent change was noted in the left lung. Some of the hilar and mediastinal lymph nodes were partly replaced by neoplastic tissue, as were both adrenal glands. The brain weighed 1,500 gm. There were neoplastic nodules in the frontal, parietal, and occipital areas of both cerebral hemispheres. There were tentorial pressure grooves over the uncus on the right and a marked cerebellar pressure cone. Transverse cut surfaces of the midbrain anterior to the pons showed the brain substance compressed, with areas of hemorrhage. Horizontal cut surfaces of the cerebellar hemispheres revealed a neoplastic nodule, 1.4 cm. in diameter, in the center of the right hemisphere. On coronal cut surfaces of the cerebral hemispheres at the level of the optic chiasm, neoplastic areas involved the right temporal lobe, 4×3 cm., and the lenticulate nucleus, 1.5 cm. in diameter. These pushed the third and lateral ventricles from right to left (Fig. 7). On parallel cut surfaces 3 cm. posteriorly, neoplastic areas were observed in the

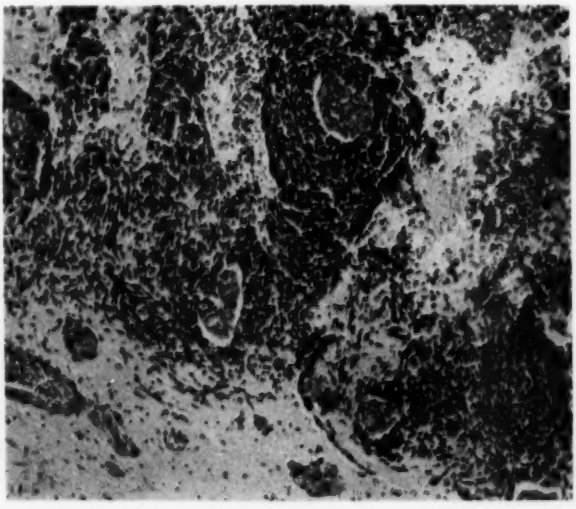


Fig. 8.—The microscopic structure is reserve-cell carcinoma, as shown in cerebral metastasis. × 100.

left thalamus, 1.5×1 cm., and in the right temporal area, 2×1.5 cm., just below the cavity of the posterior horn. Still another nodule was present in the right parietal area, 1 cm. in diameter. On cut surfaces 5 cm. posterior to the anterior poles of the frontal lobes neoplastic areas involved most of the medial frontal gyrus of the left frontal lobe. On cut surfaces 4 cm. posteriorly the white matter in the right parietal and occipital lobes was involved.

Microscopic structure of the neoplastic tissue in the brain was that of reserve-cell carcinoma (Fig. 8). Pertinent findings in the anatomic diagnosis were scar of operation: lobectomy, right lower lobe, for carcinoma of lung; recurrent carcinoma, reserve-cell, of lung, right, with metastasis to regional lymph nodes, adrenal glands and brain, with tentorial herniation, left, and hemorrhage into mid-brain; nephrosclerosis, arteriolar; cardiac hypertrophy and dilatation; emphysema of lung, left; chronic passive hyperemia of viscera; pneumonia, focal, left; thrombus, organizing, in pulmonary artery, right; cystitis, acute.

Comment

The data presented provide additional information about the biologic behavior of carcinoma of the lung. Of the 3,000 patients examined, 2,065 died after the age of 50, and of these, 284 had carcinoma of the lung, comprising 78% of the 363 patients with carcinoma of the lung. The greatest frequency, 16.7%, was in the sixth decade. The data are similar to those recently reported.[2,3]

Intracranial involvement was observed in over 38% of the brains examined, the highest percentage ever recorded.[4-6] Involvement of the brain was exceeded only by metastasis to lymph nodes, liver, and adrenal glands. Furthermore, intracranial involvement occurred more frequently before the age of 50 and significantly less after 50.

The belief that the cellular structure of carcinoma of the lung can be used to predict the course of the disease is not entirely true. In each histologic group there is a range of variations in cellular pattern, degree of differentiation, rapidity of growth, and the amount and kind of stroma induced. Regardless of the cell type, carcinoma of the lung may grow slowly or rapidly. The speed of growth is apparently governed by factors other than the cellular pattern. Therefore, study of the cellular structure of the individual carcinomas of the lung is of importance in exploring their behavior.[7-11]

The concept that all carcinomas of the lung originate from the same cell, the reserve-cell, permits an understanding of the behavior of each cell type.[12,13] The reserve cells, which appear to be the parent cells of all carcinomas of the lung, are at the bottom of the epithelial cell layer lining the bronchial tree. They are the only epithelial cells here still capable of multiplication. The reserve cells replenish the columnar and goblet cells when they are spent or injured. In the process of cell division, and presumably under the influence of some carcinogenic agent, one or more reserve cells acquire malignant properties and become cancer cells. It is yet undetermined under what influence or influences the dividing reserve cell gives rise to cancer cells. If the reserve cell that divides into cancer cells has progressed toward differentiation into columnar cells, the carcinoma is of the columnar-cell type. If the reserve cell divides into cancer cells when its potential to become a squamous cell is dominant, the carcinoma is of the squamous-cell type. If the reserve cell divides into cancer cells while it is uncommitted, it reproduces itself, and the resulting carcinoma is of the reserve-cell type (that is, undifferentiated). Thus, the cellular pattern appears to depend on the direction and the degree of differentiation of the reserve cell at the time it gives rise to cancer cells. Under physiologic conditions, the reserve cell multiplies for the purpose of replacing the top cells lining the bronchial mucosa. The same factors or agents that accelerate or interfere with the normal multiplication of reserve cells may be responsible for the carcinogenesis. The behavior of the carcinoma thus induced seems to depend not on the particular pattern formed by the cells but on the inherent

characteristics of the cancer cell. This concept of the cellular origin of carcinoma of the lung may aid in comprehending its biologic behavior.[14]

In our series of carcinomas of the lung, about 25% were reserve-cell, over 50% were squamous-cell, and the rest were columnar-cell or mixed-cell carcinomas. In each group there were slowly growing or rapidly growing neoplasms.

The manner in which the cancer cells reach the brain is not entirely clear,[15] nor is there any explanation why the cell type appears to bear no significant relationship to intracranial metastasis except that columnar-cell carcinomas metastasizing to the brain were relatively high [10] and that over one-half of the carcinomas involving the hypophysis were of reserve-cell type. Also, among other sites of metastasis, notably the liver, adrenal glands, pancreas, and spleen, the incidence of metastasis from reserve cells was relatively high. The reasons for the preference of the reserve cells for these sites of metastasis need further investigation.

After the growth is detected, the duration of the carcinoma from its inception to the death of the patient may be only estimated because the telltale clinical signs and symptoms appear only after the carcinoma of the lung is well advanced.[16] Survival time depends on the interplay of the behavior of the growth and the resistance of the host, local and constitutional. If curative measures are to be effective, obviously the growth must be recognized early, since the patients may present themselves with central nervous system involvement before attention is drawn to the primary site, the lung. The presenting complaint in nearly one-fourth of our patients with intracranial metastasis suggested central nervous system involvement. This points out the urgent necessity of a thorough neurologic examination before surgical intervention is contemplated in patients with carcinoma of the lung.[17]

Summary

The clinical histories and observations at necropsy were surveyed of 363 consecutive male patients with carcinoma of the lung, in 338 of whom the brain was included in the necropsy. Intracranial involvement was recorded in over 38% of the brains examined and was exceeded in frequency only by metastasis to lymph nodes, liver, and adrenal glands. Carcinoma of the lung involved the brain more frequently before the age of 50 years and significantly less after 50. The cell type appeared to bear no significant relationship to intracranial metastasis except that columnar-cell carcinomas metastasizing to the brain were relatively high and that over one-half of the carcinomas involving the hypophysis were reserve-cell.

Nearly 10% of the patients examined had first had signs and symptoms of central nervous system involvement. These comprised nearly one-fourth of the patients with intracranial metastasis.

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Myocardial Infarction in Man and Experimental Animals

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Myocardial infarction in man is usually caused by occlusive coronary thrombosis occurring at the site of an arteriosclerotic plaque. In the past the tendency has been to regard the presence of the plaque as all important in the etiology of coronary thrombosis and to ignore or belittle other factors that may be involved.

However, we submit the hypothesis that in most instances of coronary thrombosis two factors are involved in the etiology: (1) a *local factor* (atherosclerosis) and (2) a *hematological factor* (antifibrinolytic or procoagulative or both). Some fragments of evidence obtained from the study of man that support the above hypothesis are as follows: 1. Autopsies reveal far more persons with advanced atherosclerosis without occlusive thrombosis than with, suggesting that something more than the local lesion is needed to provoke occlusive thrombosis. 2. It is not uncommon to find coronary thrombosis in the presence of relatively mild atherosclerosis, and this occurrence is most easily explained by the presence of a hematological factor. 3. In Uganda, East Africa, the incidence of pulmonary thromboembolism in 634 Negroes 40 to 100 years old was only 2.4%, and the incidence in all other sites, including the coronary arteries, was 0.2%.* [1] The virtual absence of coronary thrombosis in this group as compared with an incidence of 22% in an age- and sex-matched group of an equal number of patients at Barnes Hospital, in St. Louis, might be accounted for on the basis of insignificant atherosclerosis (local factor); but since there is no reason to believe that atherosclerosis is associated with pulmonary thromboembolism as a local factor, some other mechanisms (hematological factor) involved in thrombosis must also be altered. 4. In certain areas in which environmental conditions were radically altered during World War II, a sudden decline in the incidence of coronary thrombosis and myocardial infarction occurred.[2] It seems unlikely that the underlying arteriosclerosis could have been altered rapidly enough to account for the speed of the decline, and change in a hematological factor is suggested.

The evidence from man (as presented above with regard to the necessity for two factors in the production of coronary thrombosis) is as yet fragmentary, but that obtained from animals is striking. In the last 50 years arteriosclerosis has been produced in many thousands of animals by diets containing large quantities of cholesterol with or without adjuncts, such as thiouracil. The number of arterial thromboses and infarcts reported in animals with cholesterol-induced arteriosclerosis, prior to our experiments, can be counted on the fingers of one hand.[3,4]

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* We are indebted to Dr. J. N. P. Davies, of Makerere College Medical School, Kampala, Uganda, for permitting us to examine his autopsy records.

Thus it seems virtually certain that in such animals the local factor was not enough to produce thrombosis but that some other factor must also have been present.

The purpose of the experiments to be reported herein was to search for a dietary means of providing the hematological factor that we had postulated was necessary for thrombosis. If such a means was found, we proposed to test its effectiveness by attempting to produce coronary thrombosis and myocardial infarction in animals with cholesterol-induced arteriosclerosis.

From our morphologic observations on pulmonary thrombi in man[6] and in animals,[8] we suspected a close affinity between lipids and thrombi. Hence it seemed reasonable to suspect that fats might influence thrombosis. Because of the extreme rarity of thrombi in cholesterol-fed animals, we were inclined to consider cholesterol as relatively unimportant in influencing the hematological factor in thrombosis.

In looking about for a simple approach by which to test the effect of various lipids on thrombi, our attention was directed to a method developed by Harrison,[7] and Wartman[8] and others for producing pulmonary arteriosclerosis by repeated intravenous injections of blood clots in rabbits. The lesions thus produced by the organization of thrombi contained little or no fat, but in all experiments the rabbits had been fed ordinary Rabbit Chow, which is very low in fat (usually about 2%). It seemed to us an ideal situation for testing the effect of various added dietary fats on at least one phase of the clotting mechanism, i.e., the fibrinolytic system.

Over the past five years we have performed series of experiments testing the effect of various dietary fats on thromboembolic-induced pulmonary vascular lesions in the rabbit. From these experiments the following pertinent observations regarding the rabbit have emerged: 1. Intermittent or daily meals of butter or margarine markedly increase the yield of thromboembolus-induced plaques in the pulmonary arteries.[9] 2. The above increase is due, at least in part, to interference with the fibrinolytic system in the rabbit's blood, and this is a general hematological effect, which can be demonstrated in the test tube.[10] 3. Meals of corn oil or of pure cholesterol (given under conditions comparable to those in which butter and margarine were used) have had no demonstrable effect on the yield of thromboembolus-induced lesions.[11,12] A close affinity between fat and thrombi was demonstrated, as indicated by finding a large amount of fat in many thrombi of rabbits receiving large daily supplements of dietary fat.[6] But perhaps even stronger evidence regarding affinity was the finding of fat in some thromboembolic lesions (and nowhere else in the vascular system) in rabbits receiving no lipid supplements but subsisting only on Rabbit Chow containing 2% fat.[9,11]

The above experiments dealt exclusively with clots formed outside the body. Our next step was an attempt to produce thrombi within the intact vascular system. In planning a dietary experiment that might result in intra-arterial thrombosis, it was decided to base the choice of diets on the hypothesis that two factors (local and hematological) would be needed. The obvious choice for the production of the *local* factor was cholesterol; chosen for the ***hematological*** factor were several fatty substances whose antifibrinolytic properties were known or suspected from our previous experiments. It seemed possible that, when the local factor was present, small mural thrombi might be formed frequently but that, in the presence of an intact fibrinolytic system, they were lysed almost as soon as they were formed. Hence introduction of an antifibrinolytic factor might result in the retention of small, nonocclusive thrombi and their build-up into large, occlusive thrombi.

For our initial attempts to produce thrombosis, rabbits were selected but were abandoned because of difficulties in getting them to eat the desired diet. Next we utilized the rat. In order to produce significant arteriosclerosis in the rat, it is necessary to feed thiouracil, as well as cholesterol.[3]

Several groups of rats were established on a diet containing cholesterol and thiouracil and other constituents in quantities known to result in the production of arteriosclerosis (local factor) with only rare infarcts.[3,4] To the diet of some of the groups we added substances, such as butter or lard, having known or suspected antifibrinolytic properties (hematological factor).

The results of these experiments exceeded all expectations. In the initial experiment, already reported,[13,14] 6 of 10 rats in one group and 4 of 10 in each of two other groups developed arterial thromboses with myocardial or renal infarcts or both. Subsequently, the experiment has been repeated six times with and without variations in the dietary components. We have continued to find significant numbers of infarcts, though the over-all incidence is somewhat less than in the initial experiment (now about 20%).

The diet that has been used in the largest number of rats is given in Table 1. The basic constituents of this particular diet, other than ordinary food requirements, are cholesterol, thiouracil, bile salts or their derivatives (to enhance absorption of cholesterol), and 40% butter. Thus far, as indicated in Table 2, 218 rats have received this diet, and of these, 43 (20%) have developed myocardial or renal infarcts or both. Also, an additional 334 rats have received variations of the infarct-producing diets, and of these, 45 (13%, with a range of 3% to 40% in the groups) have developed infarcts. These experiments will be reported in detail elsewhere, but it should be emphasized here that butter is not the only fatty substance that has been associated with infarcts. Several other saturated fats have had a similar effect, and, indeed, occasional infarcts have developed in cholesterol-thiouracil-fed groups in which only choline was altered. However, the numbers in the latter category are too small to warrant conclusions.

TABLE 1.—*Sample Infarct-Producing Diet* *

Ingredient	Percentage by Weight
Casein	20.0
Sucrose	20.7
Butter	40.0
Cholesterol	5.0
Sodium cholate †	2.0
Propylthiouracil	0.3
Celluflor (cellulose flour)	5.0
Salt mixture ‡	4.0
Vitamin mixture §	2.0
Choline chloride ‖	1.0

* This particular diet was given to 218 rats and resulted in a 20% incidence of infarcts. Fourteen other infarct-producing diets have been used.

† In 50 rats bile salts were substituted for sodium cholate.

‡ This salt mixture is the Wesson modification of the Osborne-Mendel salt mixture (*Science* 75:339, 1932).

§ Each kilogram of the vitamin mixture contained the following constituents triturated in dextrose: vitamin A concentrate, 4.5 gm. (200,000 units per gram); vitamin D concentrate, 0.25 gm. (400,000 units per gram); alpha-tocopherol, 5.0 gm. ascorbic acid, 45.0 gm.; inositol, 5.0 gm.; menadione, 2.25 gm.; p-aminobenzoic acid, 5.0 gm.; nicotinic acid, 4.5 gm.; riboflavin, 1.0 gm. pyridoxine hydrochloride, 1.0 gm.; thiamine hydrochloride, 1.0 gm.; calcium pantothenate, 3.0 gm.; biotin, 0.02 gm.; folic acid, 0.09 gm.

‖ Choline chloride in 1% solution was given in some experiments and in 0.2% solution in others, but no differences were noted between these groups.

TABLE 2.—*Summary of Incidence of Myocardial or Renal Infarcts Among 552 Rats Fed Infarct-Producing Diets*

Type of Diet	No. of Rats	No. with Infarcts *
Butter-cholesterol-thiouracil diet of Table 1	218	43 (20%)
Twenty other infarct-producing diets	334	45 (13%) †

* Myocardial or renal or both.

† Range 3%-40%.

The infarcts and thrombi in the hearts and kidneys of these rats are similar in size, location, and gross and microscopic appearance to those found in man (Fig. 1). The most remarkable anatomic feature is that thrombosis has always occurred in arteries in the stage of lipid infiltration before significant plaques had developed (Fig. 2). In man, actual atheromatous plaques are usually present before the development of occlusive thrombosis.

These dietary experiments were based on what may be called the "two-factor" theory of the etiology of coronary thrombosis, but our success in producing thrombosis does not mean that the validity of the theory has as yet been proved. However, the minimal nature of the local lesions in our rats and

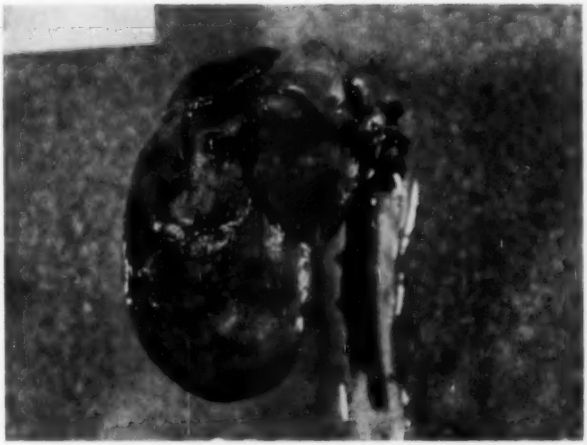

Fig. 1.—Gross photograph of a large recent infarct involving practically the entire lateral wall of the left ventricle in a rat. The infarcted area of myocardium is seen as a pale, mottled zone, which extends from the base of the heart to the apex. A large mural thrombus was also present on the endocardium, overlying the infarct.

the wealth of experience, going back half a century, indicating that even large, extensive local lesions practically never result in thrombosis in animals make it virtually certain that a hematological factor was involved. In these experiments it is the role of the local factor (lipid infiltration) in the production of the thrombi that is open to some question. However, we have not as yet produced infarcts in rats in which the hypercholesteremia regimen has been omitted and only large supplements of saturated fats have been given; this at least suggests that the local factor is necessary.

Although it seems certain that a hematological factor is involved in these experiments, it is less certain that the factor is simply an antifibrinolytic substance. It is quite possible that an increased tendency to clot is also present. We have not as yet completed our investigation of this aspect in our rats, but others have shown in man that the feeding of certain dietary fats alters coagulation times in the test tube.[16]

Of utmost concern is the dietary source of the hematological factor in coronary thrombosis that we seem to have demonstrated in our rats. Evidence from our experiments to date suggests that it is in or produced by meals of butter, lard, and certain hydrogenated fats, and it may be associated with many other materials. It is

Fig. 2.—The occlusive thrombus of a coronary artery found in the heart shown in Figure 1. Note that no intimal lesion is present. However, stains for lipid commonly revealed lipidosis of arterial walls, principally of the media. The fibrin thrombus is attached to the vessel wall, and scattered fibroblasts indicate early organization. Hematoxylin and eosin; × 420.

tempting to think of the factor in the diet as a specific substance because then, if it proved to be important in man, it could perhaps be removed without radically altering the diet. If it is simply a general property of many foods, the problem is more difficult.

Caution is always necessary in attempting to apply the results of experiments in quadripeds to man. Further studies must be made before the problem is clarified in the rat and the relation to disease in man determined. However, we believe the dietary production of myocardial infarction in the rat provides an important new tool for investigators.

Thus far our discussion has centered principally about the etiology of the proposed *hematological factor*, with only brief mention of the etiology of the *local factor*. In cholesterol-thiouracil-fed rats the local lesion is almost entirely a result of deposition of cholesterol in or on arterial walls. Most investigators postulate a similar etiology for atherosclerosis in man,[16] thus making it possible for them to explain arteriosclerosis and its complications in man entirely in terms of cholesterol levels in the blood—i.e., cholesterol levels rise in blood; arterial plaques are formed principally as a result of deposition of lipids; occlusive thrombosis occurs because of the presence of the local lesions. Duguid[17] presently champions a theory that is almost diametrically opposed—i.e., arterial plaques are formed principally as a result of deposition of mural thrombi; organization and degeneration of the thrombi occur (with fat appearing as a purely secondary feature); occlusive thrombosis occurs simply as a progression of the local lesion. We suggest that neither of these theories takes into account all of the known facts. We have submitted evidence herein that seems to indicate a close association between dietary fat and the development of occlusive thrombi. On the basis of the same evidence plus long observation of arterial plaques in all stages in man, we believe that as a practical working hypothesis facts and thrombi are inextricably associated in the development of human arteriosclerosis—i.e., in man arterial plaques are formed principally as a result of deposition of a combination of lipids and thrombi; organization and degeneration follow; occlusive thrombosis occurs on the local lesions; antifibrinolytic and/or procoagulative effects of dietary fat are involved in all stages. This dual concept of the etiology of arteriosclerosis is in accord with most or all of the established facts presented by both the "pure-cholesterol" and the "pure-thrombotic" school.

Summary

In the past 50 years arteriosclerosis has been produced in many thousands of animals by feeding cholesterol with and without adjuncts, such as thiouracil. Only in extremely rare instances has thrombosis and infarction developed in animals with cholesterol-induced arteriosclerosis. On the basis of such experiments and observations from studies of human autopsies, it is postulated that two factors are involved in arterial thrombosis: (1) a *local factor* (arteriosclerosis) and (2) a *hematological factor* (either antifibrinolytic or procoagulative or both). We searched for dietary substances that might influence the hematological factor and, in experiments involving the intravenous injection of clots into rabbits, demonstrated that several dietary fats (butter and margarine) have an antifibrinolytic effect, whereas others (corn oil and pure cholesterol), under similar conditions, do not.

Food substances with an antifibrinolytic effect could likely provide the hematological factor necessary to produce progression of intra-arterial thrombi, which might frequently form on arteriosclerotic lesions but would quickly lyse in the presence of an intact fibrinolytic system. Therefore, an experiment was performed with rats in which a cholesterol-thiouracil regimen was given to produce the local factor (arteriosclerosis)

and large quantities of butter or other saturated fats were provided to produce the hematologic factor. Rats thus fed developed arterial thromboses with myocardial and renal infarction with significant frequency (43 of 218 rats on one diet). The infarcts and thrombi are similar in every respect to those in man. However, the thrombi have usually developed in the stage of lipid infiltration of arterial walls, before actual plaques have formed, suggesting that a hematological factor is of primary importance in the formation of the thrombi.

Further experiments must be performed before the mechanism of thrombosis in these rats is elucidated and the significance for man determined.

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Malignant Papillary Cystadenoma Lymphomatosum

Report of a Case, with a Brief Review of the Literature

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Papillary cystadenoma lymphomatosum (adenolymphoma) is an uncommon parotid tumor. Chaudhry and Gorlin [1] collected 357 authentic cases from the world literature, and 192 additional cases have been described (Bernier and Bhaskar [2]; Kahler and Pallette [3]; Marshall and Uram [4]; Moyse, Castelain, and Castelain,[5] and Azzopardi and Smith [6]). Papillary adenolymphoma consists of two histological components, one epithelial, the other lymphoid. Malignant transformation involving either of these components has been infrequently reported in the past. Foote and Frazell [7] were, however, unable to accept as proved any of these examples of primary malignant change. This case report concerns a patient who suffered from a papillary adenolymphoma which we believe to have become carcinomatous.

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Report of Case

The patient, a 67-year-old Eskimo man, was first seen in 1948. He complained of a swelling extending from the right auditory meatus almost to the angle of the jaw. This had been increasing slowly in size in the previous 18 months. He gave the history that a similar swelling had been removed from the same area about 20 years earlier.

First Biopsy (1948).—Gross appearances revealed a cyst (3×2×2 cm.), containing mucoid fluid, and also an attached firm mass of similar size, which was composed of smaller cysts, exuding mucoid fluid. The mass appeared to be encapsulated.

Histologically, the cyst is surrounded by a fibrous wall without evidence of any epithelial lining. The solider mass is surrounded by fibrous connective tissue, which contains prominent lymphatic channels. The tumor is composed of glandular acini, lined by two or more layers of epithelial cells. The epithelial cells are moderately eosinophilic, faintly granular, and show little anaplasia. In many areas they are arranged in a papillary pattern. The contents of the acini are strongly eosinophilic and somewhat granular. A lymphoid stroma containing active

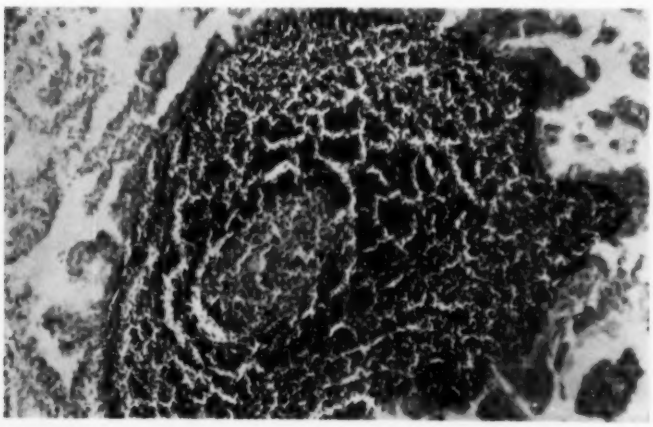

Fig. 1.—Tumor removed at first biopsy (1948). The epithelium is multilayered and papillary. It is immediately adjacent to the lymphoid stroma. Hematoxylin and eosin stain; reduced to 60% of mag. × 200.

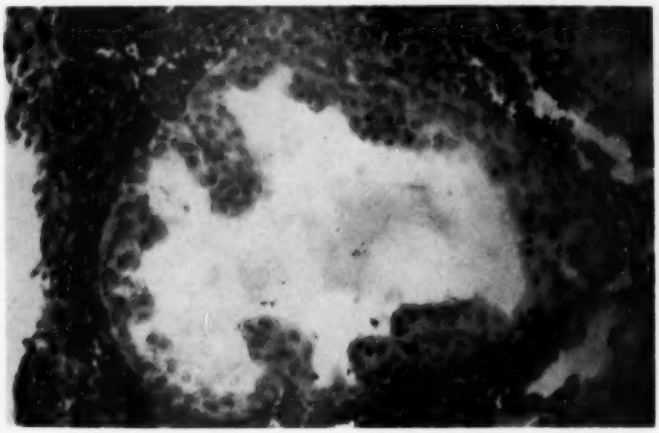

Fig. 2.—Different area of same section as that in Figure 1. The epithelium has a glandular pattern. Hematoxylin and eosin stain; reduced to 60% of mag. × 300.

germinal centers is immediately adjacent to the epithelium (Figs. 1, 2, and 3). The tumor was considered to be a benign adenolymphoma.

The patient was not seen again until August, 1956. He then had a mass (8×5×5 cm.) which seemed to be cystic and was situated below the right mastoid process and deep to the sternocleidomastoid muscle. A radical neck dissection was done, and the tumor was removed.

Second Biopsy (1956).—The specimen weighed 100 gm. The material was partly reddish-brown and fibrous and partly adipose. Cystic areas were present, from which a hemorrhagic fluid exuded.

Histologically, there is a roughly circular mass, consisting of a central papillary tumor surrounded by a peripheral shell of lymphoid tissue, in which are embedded epithelial islets similar to the central papillary mass. The epithelium of this tumor is more pleomorphic than that of the specimen removed in 1948. In some areas it is pale pink and formed by small cubical cells. In others it is deeply eosinophilic and composed of large cells with deeply staining nuclei. In a few areas the epithelium consists of two irregular rows, the more pyknotic cells being near the lumen (Fig. 4). The spaces lined by the epithelium contain pink-staining, finely granular material and mucin. The mucin stains (periodic acid-Schiff [PAS] and Alcian blue) are intensely positive immediately adjacent to the lumen, giving a "pseudo-brush-border" appearance to the lining columnar cells. Part of the tumor is surrounded by a fibrous capsule lined by

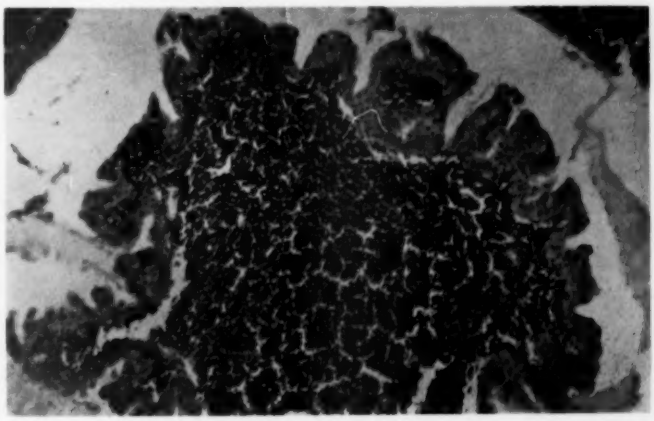

Fig. 3.—Different area from same section as that in Figure 1. The lymphoid stroma adjacent to the epithelium contains a germinal center. Hematoxylin and eosin stain; reduced to 60% of mag. × 200.

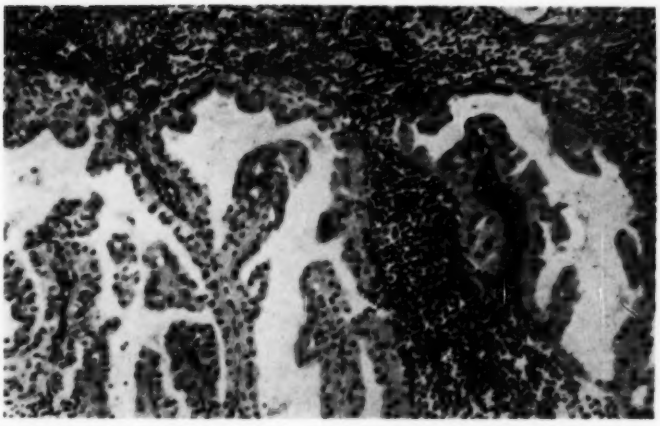

Fig. 4.—Material from second biopsy (1956.) The glandular epithelium is double-layered in some areas and is immediately adjacent to lymphoid stroma. Hematoxylin and eosin stain; reduced to 60% of mag. × 200.

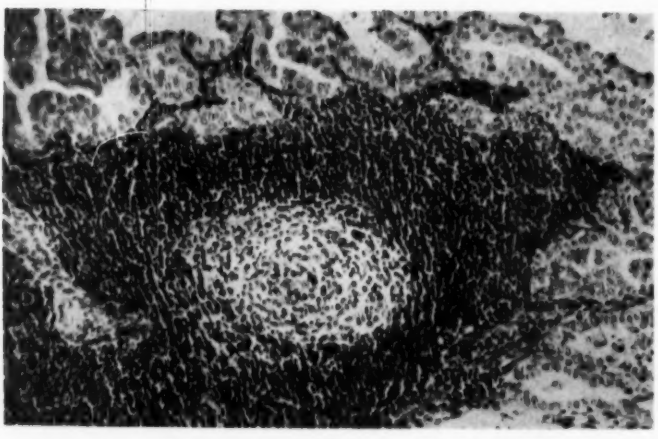

Fig. 5.—Different area from same block as Figure 4. The lymphoid stroma adjacent to the epithelium contains a germinal center. Hematoxylin and eosin stain; reduced to 60% from mag. × 200.

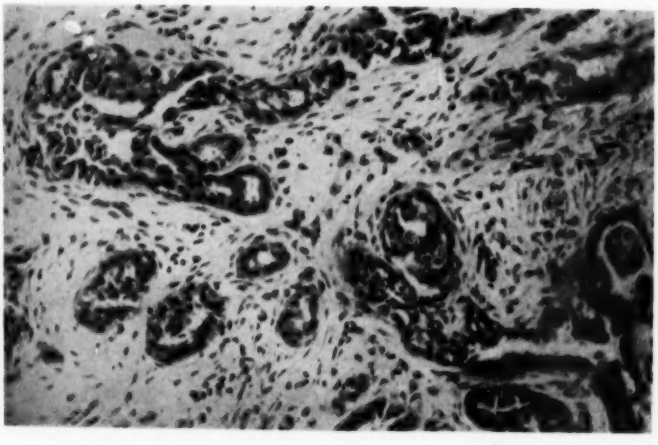

Fig. 6.—Fibrovascular connective tissue surrounding the recurrent tumor shown in Figures 4 and 5. There is infiltration by small irregular acini. Hematoxylin and eosin; reduced to 60% of mag. × 200.

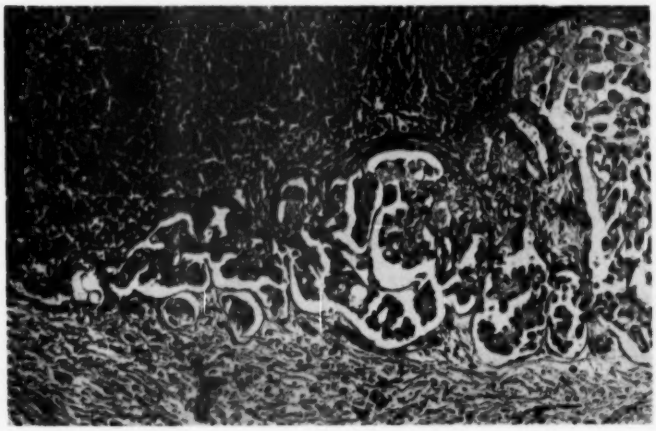

Fig. 7.—Papillary metastatic deposit in peripheral sinus of a cervical lymph node obtained at same operation as material shown in Figures 4 and 5. Hematoxylin and eosin; reduced to 60% of mag. × 200.

epithelium similar to that of the papillary areas. In the lymphoid stroma germinal follicles can be seen (Fig. 5), and sebaceous cells are also present. Parts of the capsule of this tumor and the surrounding fibrovascular connective tissue show infiltration with small, irregular acini formed by anaplastic cells (Fig. 6). These acini contain some mucin but no pink material. The epithelium of this part of the tumor has no papillary arrangement. In the peripheral sinus of a cervical lymph node there is a deposit of more pleomorphic papillary epithelium (Fig. 7).

In September, 1956, the patient was given radiotherapy to the neck (2,000 r). In February, 1957, some thickening of the upper end of the scar was noted, and in June a further course of radiotherapy was given to the recurrent tumor in this area. A swelling behind the angle of the mandible appeared in September, 1957, and in December there was, in addition, some generalized induration in the parotid area. Apart from a stabbing pain at the angle of the right jaw, the patient had no complaints. His blood pressure was 210/100 mm. Hg.

In February, 1958, he complained of weakness and loss of weight. He was hoarse and had a nonproductive cough. On examination he was found to be a feeble elderly man (pulse, 84, a minute; B.P., 130/85). The facial nerve appeared to be intact. Laryngoscopic examination showed paralysis of the right vocal cord. It was felt that further radiotherapy would not be beneficial. He was, however, admitted for a course of mechlorethamine (nitrogen mustard) and cortisone. During the patient's stay in the hospital his general condition deteriorated. After several hemoptyses he became hypotensive. His temperature rose, and he became delirious. He died in March, 1958, at the age of 77. Just before death slight icterus was noted.

Necropsy Observations.—There was a scar extending from the ear to the clavicle on the right side; the upper third of the scar was indurated, hard, and bluish. The parotid area itself was nodular. There was a superficial cystic swelling, 6 cm. in diameter, just above the middle of the clavicle. This cyst was adherent to the skin. There were also two hard nodules, both about 2 cm. in diameter, in the submental and suprasternal areas. These also were adherent to the skin. No other tumor deposits were found. The thyroid gland was normal grossly and microscopically. The heart weighed 480 gm. The coronary vessels showed minimal atheroma, and the myocardium was healthy. Both lungs were edematous. The right lung, which weighed 1,150 gm., showed multiple infarcts and organizing pneumonia. The left lung weighed 500 gm., and there was patchy bronchopneumonia. The liver weighed 1,850 gm. and was yellowish brown. Its surface was smooth. Histologically there was disarray of the hepatic cells, in keeping with virus hepatitis in the recovery phase. Prostatic hypertrophy and bilateral pyelonephritis were also present.

Sections from the tumor site and two of the metastatic deposits were taken for microscopic study. No adenolymphomatous areas are present anywhere. Sections from the tumor mass at the angle of the jaw show irregular, mucus-secreting acini, embedded in densely hyalinized fibrous tissue (Fig. 8). Sections from the suprasternal metastasis show similar acini embedded in a

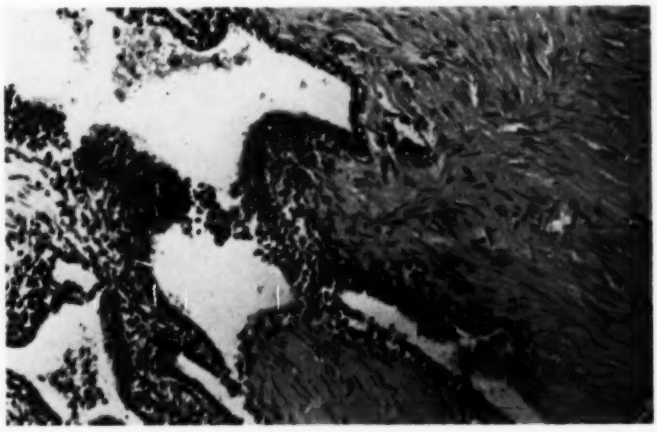

Fig. 8.—Section from mass at angle of jaw (necropsy). There are irregular acini in densely hyalinized fibrous tissue. The epithelium consists of a double layer of cells. Hematoxylin and eosin; reduced to 60% of mag. × 200.

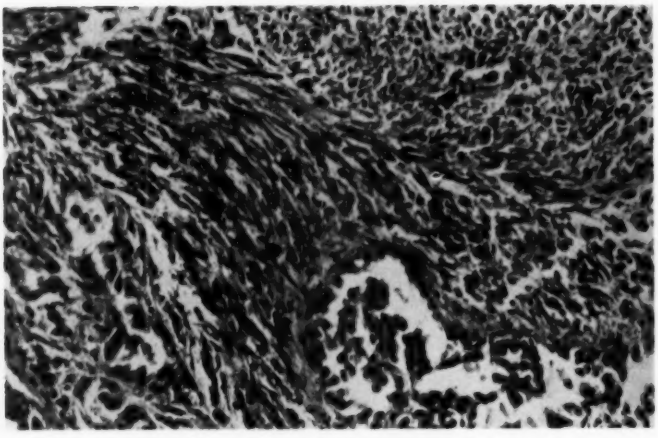

Fig. 9.—Section from suprasternal mass (necropsy). Both the epithelium and the stroma are more anaplastic than the tissue in Figure 8. Hematoxylin and eosin; reduced to 60% of mag. × 200.

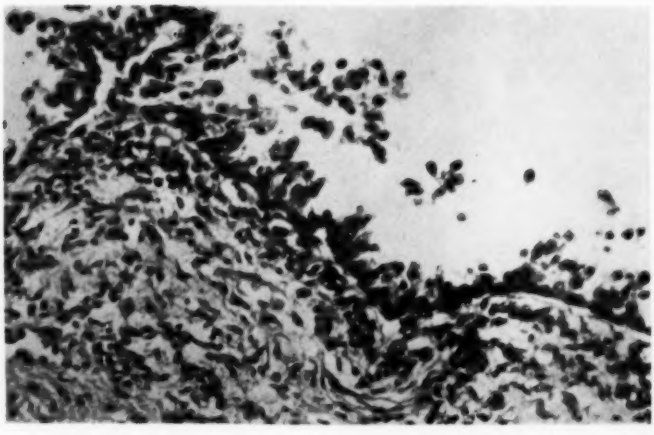

Fig. 10.—Section from cystic supraclavicular lesion (necropsy). The cyst is lined by pleomorphic papillary epithelium. Hematoxylin and eosin; reduced to 60% of mag. × 200.

very cellular stroma composed of anaplastic spindle cells (Fig. 9). Sections from the cystic supraclavicular lesions show a space lined by similar, but rather more papillary, epithelium (Fig. 10). The surrounding fibrous connective tissue has some highly cellular areas in which a few bizarre giant cells can be seen.

Comment

The histological structure of the tumor removed in 1948 (Figs. 1, 2, and 3) is that of a benign papillary cystadenoma lymphomatosum. The arrangement of the epithelium is, however, slightly more irregular than is usually seen, and it is intriguing to speculate whether the histology of the neoplasm removed 20 years previously might have been more typical of the classical adenolymphoma. The location of the neoplasm and the age and sex of the patient are characteristic.[1] Recurrence of cystadenoma lymphomatosum is not uncommon. It took place in 6 out of the 49 cases of Foote and Frazell.[7]

The recurrence in 1956 in its greater part differs considerably from a typical adenolymphoma. The central core of this tumor has a papillary structure with little or no lymphoid stroma. In the peripheral area, however, the acini still have a relation to the lymphoid stroma, such as is seen in an adenolymphoma rather than in a lymph node metastasis (Figs. 4 and 5). While usually the epithelium is composed of a single layer of large red cells, there are a few areas in which the epithelium stains pale pink and has an irregular double-layered arrangement, similar to a typical papillary adenolymphoma.

The "pseudo-brush-border" appearance with mucin stains is characteristic of adenolymphoma,[6] and the presence of sebaceous cells is also consistent with this diagnosis.[7] We feel that most of the papillary areas, while undoubtedly hyperplastic, are not indisputably malignant. The papillary metastatic deposit in the peripheral sinus of a lymph node (Fig. 7) and the small, nonpapillary acini seen infiltrating the fibrous connective tissue surrounding the tumor (Fig. 6) are, however, undoubtedly malignant.

The recurrent tumor with metastases seen at autopsy in 1958 (Figs, 8, 9, and 10) is fundamentally similar to the infiltrating areas of the 1956 specimen but exhibits greater pleomorphism. The spindle-cell stromal transformation seen in Figure 9 is not uncommon in carcinoma.[8]

There are three possible interpretations of the histogenesis of this tumor. The first is that a new independent malignant tumor developed in 1956 at the site of the adenolymphoma removed in 1948. Second, it could be argued that at the site of a papillary adenolymphoma there developed a papillary adenoma which developed into a carcinoma. We believe these explanations to be unlikely, because, in spite of great variations in its histological structure, the 1956 tumor still has adenolymphomatous areas. The third possibility, which appears to us the most probable, is that the papillary adenolymphoma recurred and that its epithelial element underwent progressive malignant change.

Malignant transformation of the epithelial component of a papillary cystadenoma lymphomatosum has been reported on several occasions. Nicholson's second case[9] and Stöhr and Risak's[10] and Goedel's[11] cases are now generally believed not to show any definite evidence of malignancy.[12]

In his second case, Ssobolew[13] reported the coexistence of a papillary carcinoma with an adenolymphoma. This may have been a true malignant change in a papillary adenolymphoma, but his illustration does not prove this. Tanaka and Chen[14] reported a case of bilateral papillary cystadenoma lymphomatosum associated with mucoepidermoid carcinoma which appeared to be separate from the adenolymphoma. Thompson and Bryant[12] reported a case (Case 7) showing two separate tumors in the parotid region. One was a papillary cystadenoma lymphomatosum. The other was considered to be carcinoma. Through the courtesy of

Dr. A. J. French, we were able to review the sections from this case. We agree with Dr. French that there is no definite evidence of malignancy in the specimen. The lesion thought to be carcinoma by Thompson and Bryant seems to us to be a mixed salivary-gland tumor. Follow-up of this patient in February, 1958, indicated no recurrence.

Hanford [15] reported a patient (Case 2) who developed a squamous-cell carcinoma of the neck three years after a papillary cystadenoma lymphomatosum. Through the courtesy of Dr. G. P. Vennart, we were able to review the sections from this case. We agree with Thompson and Bryant [12] that they do not prove the origin of the squamous-cell carcinoma from the original adenolymphoma. Lederman [16] reported a patient with a somewhat similar history. In this case the original diagnosis of papillary cystadenoma lymphomatosum was not proved by biopsy, and the patient was given radiotherapy.

Association of a papillary cystadenolymphoma lymphomatosum with a malignant lymphoma has been reported by Martin and Ehrlich [17] and Rekers,[18] but in neither report was there histological proof that the lymphoma involved the parotid tumor.

Review of the literature thus confirms the opinion of Foote and Frazell [7] that none of the previously reported instances of malignant change in cases of papillary adenolymphoma can be considered proved. Bernier and Bhaskar [2] consider cystadenoma lymphomatosum to be an epithelial tumor occurring in a lymph node. If this is accepted, malignant change need not involve the lymphoid stroma. Although the evidence is not conclusive, it is thus quite possible that in some previously reported cases, particularly those by Ssobolew [13] and Hanford,[15] a papillary or squamous-cell carcinoma may have arisen from an adenolymphoma. Chaudhry and Gorlin [1] point out how unsatisfactory is the long-term follow-up of cases reported so far. On the other hand, in some patients with salivary-gland carcinoma a previous history of adenolymphoma may have been missed. In our case the original (1948) tumor was undoubtedly an adenolymphoma. Ten years later the patient had a carcinoma in the parotid region with metastases to the neck. We consider that the material from the intervening biopsy, in 1956, shows that the adenolymphoma recurred and underwent malignant change. This case differs considerably from any previously reported. We believe, however, that further study of cases of papillary cystadenoma lymphomatosum with sufficient follow-up may well bring to light similar examples of malignant change.

Summary

A recurrent papillary cystadenoma lymphomatosum is reported which we believe to have undergone malignant change, because of spread to the peripheral sinus of a cervical lymph node, infiltration of the surrounding fibrous connective tissue, and metastases to supraclavicular, submental, and suprasternal areas.

The literature concerning this tumor is reviewed. It is concluded that malignant change has not been proved in any of the previously reported cases of papillary cystadenoma lymphomatosum.

We wish to thank Prof. R. A. Willis, who kindly examined the material from this case and agreed with the diagnosis of malignant adenolymphoma. We are also grateful to Dr. A. J. French, of the University of Michigan, and Dr. G. P. Vennart, of Columbia University, who gave us access to sections from previously reported cases, and to Mr. C. S. Brindle, who took the photomicrographs.

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News and Comment

ANNOUNCEMENTS

Fourteenth Annual Symposium on Fundamental Cancer Research.—The University of Texas M. D. Anderson Hospital and Tumor Institute announces the 14th Annual Symposium on Fundamental Cancer Research to be held Feb. 25, 26, and 27, 1960. The subject of the symposium will be "Cell Physiology of Neoplasia." Additional information may be obtained from the Editorial Office, The University of Texas M. D. Anderson Hospital, Texas Medical Center, Houston 25, Texas.

Third Congress of the International Academy of Pathology.—The International Academy of Pathology holds its Third Congress in London, England, June 20-25, 1960. The meeting follows that of the Fourth International Congress of Clinical Pathologists in Madrid, Spain, June 13-17, 1960. All inquiries concerning the offering of papers and exhibits should be addressed to F. K. Mostofi, M.D., Secretary-Treasurer, International Academy of Pathology, Armed Forces Institute of Pathology, Washington 25, D.C.

GENERAL NEWS

Armed Forces Institute Seeks Old Instruments.—The Armed Forces Institute of Pathology, Washington, D.C., is seeking military medical material to expand the famous collections of historical items in its Medical Museum, which is one of the four major departments of the Institute, a national institution jointly sponsored by the Army, the Navy, and the Air Force. The Museum has one of the finest collections of microscopes in the world, displayed to the show the evolution of the microscope from its origin through the most recent developments in electron microscopy. Few microscopes have been added to this collection in recent years, and efforts are now being made to fill the gaps, particularly the years from 1920 to the present. The Institute will celebrate its 100th anniversary during and concurrently with the Civil War Centennial. Museum personnel are now planning the exhibits for this occasion. Through the long history of the Institute a great number of historical instruments have been assembled, but among this material is very little of Confederate Army origin. Such items particularly are being sought. Although budgetary limitations preclude the purchase of such items, it is believed that there are a great number of instruments or other items which the owners might wish to place in the Museum, where they will be carefully preserved for future generations. Any such donations would be greatly appreciated and due credit given. Persons having items they may wish to contribute are requested to write the Director, Armed Forces Institute of Pathology, Washington 25, D.C., relative to their acceptability and shipping instructions.

PERSONAL

Dr. Shields Warren Receives Honorary Degree.— Dr. Shields Warren, of Boston, received the honorary degree of Doctor of Science at the centennial celebration of Northwestern University Medical School on Sept. 29, 1959.

The Richard H. Jaffe Memorial Lecture.—Dr. Jesse E. Edwards' of Rochester, Minn., delivered the Richard H. Jaffe Memorial Lecture in Cook County Hospital, Chicago, on Sept. 16, 1959. The subject of his lecture was "Healed Bacterial Endocarditis."

DEATHS

Dr. Milton C. Winternitz.—Dr. Milton C. Winternitz, for many years head of the pathology section of Yale University School of Medicine, and later dean, died in Hanover, N.H., on Oct. 3, 1959.

Books

"Allergic" Encephalomyelitis. Edited by Marian W. Kies, Ph.D., and Ellsworth C. Alvord Jr., M.D. Price, $13.50. Pp. 590, with 257 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1959.

This symposium on a rather specialized topic is of particular interest to persons concerned with the general subject of organ sensitivity, as well as those interested in the more specific ramifications of this experimental disease in neuropathology. The topic is discussed in terms of (1) pathology, including discussions of the relationships to human disease, (2) identification of encephalitogenic materials, and (3) immunologic aspects. The contributors to the volume include most of the persons who have studied this experimental disease in Europe and America. The discussion of each major presentation is extensive and provocative. This volume can be recommended as a detailed survey of this interesting field. The book is well printed and illustrated.

The Innervation of Muscle: A Biopsy Study. By C. Coërs (*Docteur en Médecine*) and A. L. Woolf, M.D. Price, $9.00. Pp. 160, with 265 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1959.

The staining of nerve fibers and nerve endings by the intravital methylene blue method has been in experimental use since the latter part of the nineteenth century. In 1952 the senior author of this monograph applied this technique successfully to human muscle biopsy material by injecting the dye locally into surgically exposed muscle tissue before resection of the sample. Using this method in conjunction with a modification of Koelle's cholinesterase staining technique, the authors studied 450 muscle biopsy specimens taken from normal subjects, as well as from patients with a wide variety of diseases of muscle, peripheral nerves, and central nervous system. The recommended technique of muscle biopsy is described in some detail, since special care is required to obtain specimens that include motor end-plates. Except in the case of muscles with short fibers, electrical stimulation of the exposed muscle is necessary to localize those portions rich in motor nerve endings.

The staining solutions and techniques are also set forth in detail.

One chapter is devoted to a description of the histology of the normal muscular nerves and nerve endings, and this is followed by chapters describing the general pathology of these structures and the special pathology encountered in specific disease states.

There would seem to be no question that the intravital methylene blue staining technique demonstrates the fine terminal ramifications of the motor endings beautifully. The complementary application of the cholinesterase technique likewise provides a highly informative picture of the postsynaptic portion of the motor end-plate, or subneural apparatus. One might perhaps hope that a systematic study of these structures, such as has been initiated by the authors, would provide differential diagnostic criteria of a more rigorous type than those that have been yielded by conventional biopsy staining techniques. This goal, however, has not yet been reached. It would appear that the relationship between nerve ending and muscle is so intimate that even the highly specific techniques described here cannot be fully depended upon to distinguish primary myopathy from primary neuropathy.

One important deficiency in this book is the virtually complete lack of clinical information about the patient material used for the study. In most instances the biopsy material is simply placed under a heading which names the disease and gives the number of cases studied. For some of the entities discussed, such as poliomyelitis and dystrophia myotonica, this is acceptable in view of long-established and generally accepted criteria for clinical diagnosis. But for others, such as Werdnig-Hoffmann disease, infantile polyneuritis, and amyotonia congenita, one would feel somewhat more secure in judging the relationship between disease entity and histological findings if clinical information were presented also. The reader's uneasiness on this score is by no means diminished by the section placed under the heading "Carcinomatous Peripheral Neuropathy, Including Sensory Neuropathy (8 Cases)," when

the only further clinical information given is that the presence of carcinoma had not been demonstrated in seven of the eight cases.

This defect, however, is, fortunately, not directly relevant to the primary purposes of the book, which are to describe the techniques fully and to illustrate and describe the results in detail. There are 281 illustrations, most of them being superbly reproduced photomicrographs, 12 of them in color. These alone make this book well-nigh indispensable to those engaged in the study of the histology of muscle tissue in health or disease, and of great value for all who are interested in the physiology of the neuromuscular junction.

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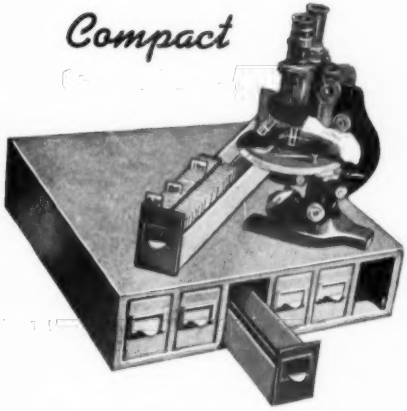

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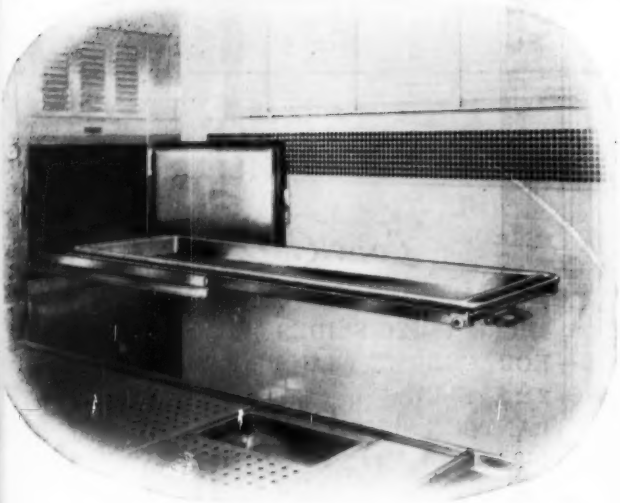

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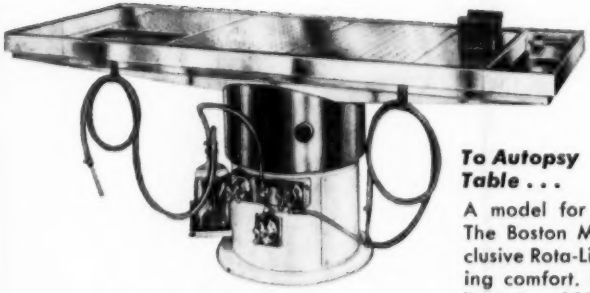

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